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

Tetraacetylethylenediamine (TAED)
(CAS 10543-57-4)

Draft

DECEMBER 2002

All rights reserved. No part of this publication may be used, reproduced, copied, stored or transmitted in any form of by any means, electronic, mechanical, photocopying, recording or otherwise without the prior written permission of the HERA Substance Team or the involved company.

The content of this document has been prepared and reviewed by experts on behalf of HERA with all possible care and from the available scientific information. It is provided for information only. HERA cannot accept any responsibility or liability and does not provide a warranty for any use or interpretation of the material contained in this publication.

1. Executive Summary

General

TAED (tetraacetylethylenediamine) is a bleaching activator which is mainly used in detergents and additives for laundry washing and dishwashing. Typical concentrations of TAED range between 1.4% and 13% in these products. The amount of TAED which is used in household cleaning products in Europe was estimated to be 61,000 t in 2001.
After starting the washing process, TAED is completely dissolved within minutes in the wash liquor and undergoes perhydrolysis in the presence of persalts such as perborate or percarbonate via triacetylethylenediamine (TriAED) to diacetylethylenediamine (DAED). A recent kinetic study of the perhydrolysis under conditions of the washing process (pH 10) has shown that TAED is converted >99% to DAED even at low temperature (23 degree C).
In this risk assessment report the parent compound TAED as well as the final degradation product DAED were assessed. TriAED was not considered as no significant concentrations arise during the perhydrolysis process.

Environment

For the Environmental Assessment it was assumed that after the washing process has been finished 99% of DAED and 1% of TAED is discharged into the sewer. A full environmental risk assessment was carried out for TAED and DAED with the modelling program EUSES using different scenarios.
TAED and DAED which have high water solubility are readily eliminated in sewage treatment plants (> 97%) and degradation in river water is rapid with half-lives of about 9d. Although TAED and DAED do not sorb strongly to dissolved and suspended matter some emissions to agricultural soil may occur via application of sewage sludge. Emissions to air can be neglected. Due to the low octanol-water partitioning coefficient of TAED and DAED bioconcentration and bioaccumulation will not occur. For the same reasons secondary poisoning and indirect exposure of humans via environment are unlikely.
TAED and DAED show low acute aquatic ecotoxicity. Sediment and soil ecotoxicity data are not available but estimations were carried out using the equilibrium partitioning method. From these data and the estimates PNECs for the different environmental compartments were derived. The Risk Characterisations for water, sediment, soil and sewage treatment plant based on the estimated PECs and PNECs show that the risk quotients for all scenarios were below 1 (acceptable risk).
.

Human Health

TAED is of very low toxicity by all exposure routes examined. Up to 2 g/kg BW there is no acute toxicity. TAED is practically non-irritating to skin and eyes and there is no evidence of a sensitizing potential by skin contact. The only effect after repeated oral and dermal dosing was reversible centrilobular hypertrophy in the liver at high doses due to the induction of metabolizing enzymes. In a 90-day whole body inhalation study no adverse effects in the rat lung, respiratory tract or nasal mucosa were observed. Biokinetic data showed that TAED is rapidly absorbed from the rat intestine and largely metabolized via diacetylation to TriAED and DAED which are excreted in the urine. Skin penetration studies indicated, that 0.13%-4.3% of pure TAED or TAED present in solutions of detergent bases can penetrate rat skin

depending on contact time. TAED was not genotoxic and not teratogenic. Chronic toxicity, carcinogenicity, fertility and late stages of developmental toxicity (from birth to sexual maturity of offspring) have not been addressed. However, based on the chemical structure and the available toxicity and kinetic data it can be expected that TAED will cause no concern with respect to these endpoints. Based on above data, the 'No Observed Adverse Effect Level' of 90 mg/kg BW/d was deduced to assess systemic TAED exposure.
There are only a few toxicity data available on DAED and they all indicate very low toxicity. DAED was not acute toxic at a dose of 2 g/kg BW when given orally and was non-mutagenic and non-sensitizing. It was rapidly absorbed from the gastroinestinal tract and excreted via urine. The 'No Observed Effect Level' of 5700 mg/kg BW/d has been reported in a 90-day rat feeding study. For all other endpoints, data on TAED can be used as bridging data.

The presence of TAED in many commonly used household detergents gives rise to a variety of possible consumer contact scenarios including direct and indirect skin contact, inhalation, and oral ingestion.
The total systemic exposure resulting from these scenarios was estimated to be 0.013 µg TAED and 0.089 µg DAED/kg BW/day. In conjunction with the NO(A)ELs for systemic exposure (90 mg TAED/kg BW/d and 5700 mg DAED/kg BW/d) the extremely high Margin of Exposures of 7,030,000 and 64,100,000 were determined for TAED and DAED, respectively, indicating no risk for human health.
On the basis of the toxicological data skin sensitization, accidental exposure of skin or eyes as well as accidental ingestion are of low concern.

It can be concluded that TAED contained in consumer washing and dish washing products as well as the amount of DAED formed during the washing process do not cause concern to human health.

2. Contents

3. Substance Characterisation

Tetraacetylethylendiamine (TAED, CAS No. 10543-57-4) is a bleaching activator in household detergents (Clariant, 1999). A small amount of the produced TAED is also used in bleaching of paper, textiles and for the generation of Peracetic acid (PAA, CAS No. 79-21-0) in disinfectants but is not considered in this HERA Assessment.

In the washing liquor, at alkaline pH and in the presence of a source of hydrogen peroxide such as perborate or percarbonate, TAED undergoes rapid perhydrolysis yielding Peracetate and Diacetylethylenediamine (DAED, CAS No. 871-78-3). The reaction is a stepwise process via the intermediate Triacetylethylenediamine (TriAED, CAS No. 137706-80-0). A recent investigation (Clariant, 2002a) shows that TriAED is only present during a short period of time whereas almost all TAED is converted to DAED (see chapter 4.1.1). DAED is not easily hydrolysed (Clariant, 2002a, Gilbert, 1992) but is readily biodegradable. During the bleaching process Peracetate oxidizes stains and is itself converted to Acetate (details see chapter 3.3). The kinetics of the bleaching process were investigated (Reinhardt et al, 1989) and the data show that it depends on temperature and pH.

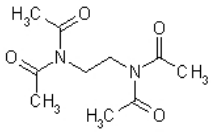
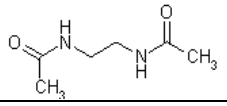
From these findings it is assumed for the Envrionmental Risk Assessement that 1% TAED and 99% DAED (but no TriAED) are discharged into the sewer when the washing process is finished (realistic worst case assumptions). This means two assessment are to be carried out, one for TAED and one for DAED. Therefore the pertinent data for TAED and DAED are summarized in the following.

As Peracetate is transformed to Acetate during the bleaching process and is itself rapidly degraded under abiotic conditions as well (ECETOC, 2001) Peracetate is not considered in this assessment. The Acetate formed from Peracetate during the bleaching is a natural constituent of living organisms which can be metabolized directly by microorganisms and is therefore not covered in this assessment either.

3.1 Chemical structure and composition

In table 3.1.1 the names, CAS numbers, mol weight and structures of TAED and DAED are given.

Table 3.1.1 Name, CAS No., mol weight and structure of TAED & DAED

Abbrev.	Name	CAS No.	Mol weight (g/Mol)	Structure
TAED	Tetraacetylethylenediamine	10543-57-4	228.25	
DAED	N,N'-Diacetylethylenediamine	871-78-3	144.17	

In table 3.1.2 the physico-chemical data of TAED and DAED are listed.

From the physico-chemical data it can be seen that TAED and DAED are highly soluble in water, have low vapour pressure and low volatility. Sorption to organic carbon is very low.

Table 3.1.2 Physico-chemical data

Parameter		Value	Reliability	Remark
Physical state	**TAED**	solid (crystall.) particle size distr.	1	IUCLID Clariant, 2002; Peractive P, Product Specification, Clariant, 2000-10-18
	DAED	Solid	1	Beilstein Online Database, BRN 1762229
Bulk density (kg/m^3)	**TAED**	550	1	IUCLID Clariant, 2002, DIN 53912
	DAED	-	-	-
Melting point (deg C)	**TAED**	152 (meas.) 186 (calc.)	1 2	IUCLID Clariant, 2002 SRC MPBPWin, 1999
	DAED	170-172 142 (calc.)	1 2	Clariant, 2002c SRC MPBPWin, 1999
Boiling point (deg C)	**TAED**	140 (2 hPa)	1	IUCLID Clariant, 2002; decomposition
	DAED	-	-	-
Vapour pressure at 25 C (Pa)	**TAED**	4.8E-06	2	SRC MPBPWin, 1999
	DAED	5.3E-04	2	SRC MPBPWin, 1999
Water solubility at 25 C (g/l)	**TAED**	1 - 2 (measured) 1000 (calc.)	1 3	IUCLID Clariant, 2002 SRC WSKow, 1999
	DAED	683 > 1000 120 (calc.)	4 1 3	Tucker, 1935 Clariant, 2002b SRC WSKow, 1999
log Kow	**TAED**	- 0.08 (meas.) -2.4 (calc.)	1 2	Warwick, 2000a SRC KOWWin, 1999
	DAED	- 1.3 (meas.) -1.03 (meas.) - 1.7 (calc.)	4 1 2	AISE, 1992 Warwick, 1992 SRC KOWWin, 1999
Koc (l/kg)	**TAED**	15 (meas.) 43 – 80 (meas.) 415 (calc.)	4 2 3	AISE, 1992 Shell, 2000 (different soils) SRC PCKOC, 1999
	DAED	25 (meas.) 16 (calc.)	4 2	AISE, 1992 SRC PCKOC, 1999
Henry coefficient (unitless)	**TAED**	7.4E-15	2	SRC HENRY, 1999
	DAED	7.0E-10	2	SRC HENRY, 1999
pH	**TAED**	5 (20 C, 1g/l)	1	IUCLID Clariant, 2002
	DAED	not available	-	-

Reliability criteria of IUCLID are used:
1 valid without restriction 2 valid with restrictions 3 not valid 4 validity is not assignable

3.2 Manufacturing Route and Production/Volume Statistics

3.2.1 Manufacturing Route

TAED is produced in a two stage process from ethylenediamine (ED) and acetic anhydride (Ac_2O). ED is first diacetylated to DAED. In the second step DAED is subsequently converted with Ac_2O via TriAED into TAED (Clariant, 1999). TAED is crystallized out of the reaction mixture, filtered, washed and dried, and if necessary also granulated. The raw materials used occur almost quantitatively in the product. Byproducts are not formed.

3.2.2 Production/Volume statistics

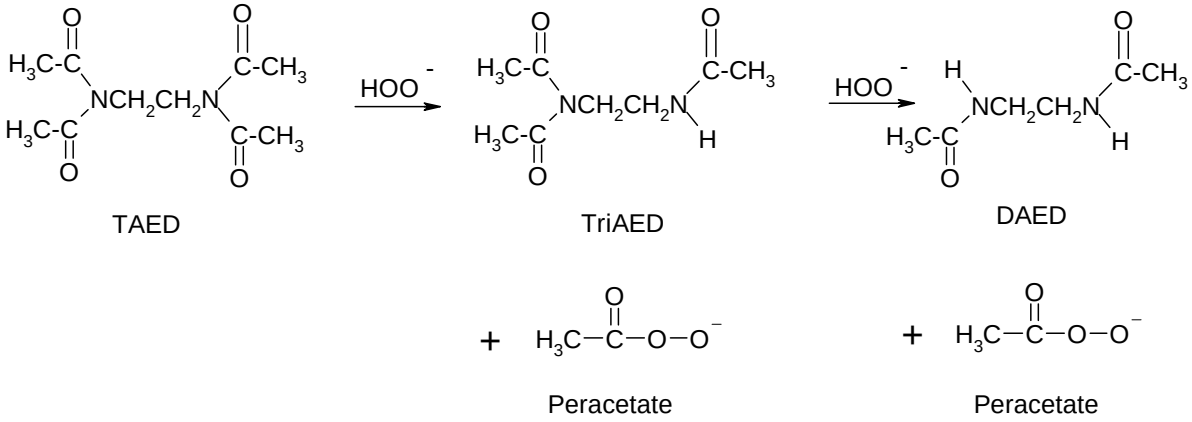
In 2000 a total of 80.000 t/a of TAED was produced in the EU and 19.000 t/a of the total was exported outside the EU. The remaining 61.000 t/a TAED was consumed in household detergents in the EU (AISE, 2002).

3.3. Use applications summary

Most of the consumption relates to the use as bleaching activator in household detergents (Clariant, 1999) but a small amount of TAED is also used in bleaching of paper, textiles and for the generation of peracetic acid in disinfectants. In this focused HERA Assessment only the use of TAED in household detergents is considered using two different release scenarios - one is the standard EU TGD (EU, 1996) release scenario for household detergents (Industry category IC 5 Personal / Domestic use, use category UC 9 Surfactants and Cleaning Agents) the other is a modified scenario according HERA Guidance Document (HERA, 2001) using more realistic release data.

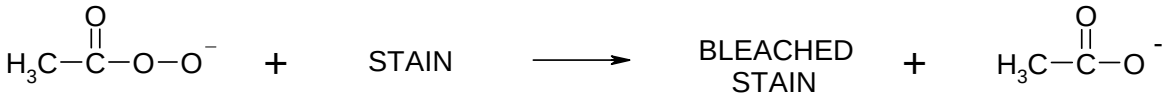
In the washing liquor, at alkaline pH and in the presence of a source of hydrogen peroxide such as perborate or percarbonate, TAED undergoes rapid perhydrolysis yielding peracetic acid (PAA) and diacetylethylene diamine (DAED). The reaction is a stepwise process via the intermediate triactetylethylene diamine (TriAED). Under European washing conditions (30 – 60 °C) the perhydrolysis is completed within 15 min.

Perhydrolysis:



PAA and its salt, peracetate, are highly efficient oxidising agents being able to bleach a number of stubborn stains (tea, red wine, food stains etc.). The bleach system also removes unpleasant odour, ensures a high hygiene standard of the washing by its antimicrobial action and contributes significantly to the overall whiteness of the laundry.

Bleach reaction:



Depending on the soiling of the laundry and washing temperature 50-100 % of the generated PAA is reduced to acetate in the bleach reaction. The remaining PAA will rapidly decompose to acetate when it comes into contact with the raw sewage.

4. Environmental Assessment

An Environmental Risk Assessment for the aquatic compartment was carried out already (Gilbert, 1992) and is used as a basis of this HERA Environmental Risk Assessment.

4.1. Environmental Exposure Assessment

As mentioned in section 3 more than 99% of TAED used in household detergents is converted to the hydrolysis product DAED already within the application process. Therefore this assessment assumes that 1 Mol-% of TAED and 99 Mol-% of DAED will be discharged to the sewer.

4.1.1. Environmental Fate

4.1.1.1 Biodegradation in Water

Aerobic biodegradation in water

Results from standard laboratory biodegradation tests

The potential of TAED and DAED to biodegrade under aerobic conditions was intensively investigated and the results are summarized in table 4.1.1.1.1.

Table 4.1.1.1.1 Aerobic biodegradation results in standard tests

Ready Biodegradab. Tests		Value (%)	Reliability	Remark/Reference
OECD 301 B (Sturm Test)	**TAED**	68-95 (28d) 79	1 2	Hoechst, 1995a, Verschueren, 2001 Unilever, 1981a
	DAED	100 (adapt.) 91	4 4	Schoeberl et al, 1988 Gilbert, 1992
OECD 301 D (Closed Bottle Test)	**TAED**	52-56 (28d)	2	Henkel, 1972a
	DAED	60 (28d)	2	Henkel, 1972b
OECD 301 E (Modif. OECD Screening Test)	**TAED**	79 (28d) 86-89 (28d)	1 2	Warkwick, 1989 Henkel, 1972c
	DAED	-	-	-
Inherent Biodegradab. Tests		**Value (%)**	**Reliability**	**Remark/Reference**
OECD 302 A (SCAS Test)	**TAED**	100	4	Gilbert, 1992
	DAED	-	-	-
OECD 302 B (Zahn-Wellens-Test)	**TAED**	95 (7d)	2	Hoechst, 1983
	DAED	95 (?)	4	Gilbert, 1992
Simulation Tests on Biodeg.		**Value (%)**	**Reliability**	**Remark/Reference**
OECD 303 A (Coupled Units Test)	**TAED**	98 (DOC)	1	Hoechst, 1995b
	DAED	-	-	-
Porous pot test (^{14}C labelled material)	**TAED**	>97* (mean)	2	not all ^{14}C in effluent may be related to TAED; Gilbert, 1992
	DAED	>97* (mean)	2	not all ^{14}C in effluent may be related to DAED; Gilbert, 1992

* total removal of ^{14}C radioactivity (ca. 30-59% 14-CO_2 and ca. 30-70% adsorbed 14-C to sewage sludge)
Reliability criteria of IUCLID are used:
1 valid without restriction 2 valid with restrictions 3 not valid 4 validity is not assignable

From these data it can be concluded that TAED and DAED are readily biodegradable.

The results from the simulation tests on biodegradability can be used directly as removal rates of the sewage treatment plant (stp) in the calculations of PEC_{water}. The results from the OECD 303A Coupled Units Tests for TAED and from the Porous Pot Test with radiolabeled materials for TAED and DAED (^{14}C acetyl and ^{14}C ethylene) show that eliminations of > 97% have been achieved.

Therefore 97% removal will be used as a realistic worst case elimination in stp for TAED and DAED in calculations later on.

Results from a River Water Die Away Test

In a river water die away test radiolabeled TAED and DAED showed rapid ultimate biodegradation (e.g. ca. 90 % $^{14}CO_2$ evolution within 21d for TAED; Unilever, 1981b and > 80% for DAED, Gilbert, 1992). Assuming a first order kinetic for the biodegradation results in a half-life of < 9d in river water (table 4.1.1.1.2).

Another study (Procter & Gamble, 1977) showed a nearly 100% removal of DAED in a River Die Away Test at 20 mg/l DAED within 7 days.

Table 4.1.1.1.2 Aerobic biodegradation results in River Water Die Away Tests

River Water Die Away Test		Half-life $t_{1/2}$ (d)	Reliability	Remark / Reference
River Water Die Away Test with ^{14}C labelled material	**TAED**	6,3	2	(1st order kinetic assumed); Unilever, 1981b
	DAED	< 9 ?	2	(1st order kinetic assumed); Gilbert, 1992
River Die Away Test (no details available)	**DAED**	ca. 1,1	4	Procter & Gamble, 1977 (half-life estimated from total elimination)

Reliability criteria of IUCLID are used:
1 valid without restriction 2 valid with restrictions 3 not valid 4 validity is not assignable

According to the EU Technical Guidance Document for Risk Assessments (EU, 1996) for readily biodegradable substances a half-life in water of 15d is assumed. Based on the data of a River Die Away Tests (Table 4.1.1.2) for TAED and DAED shorter half-lives can be derived. In the EUSES calculations for TAED and DAED half-lives of 9d in surface water were used (realistic worst case).

Anaerobic biodegradation in water

No data are available on the anaerobic biodegradation of TAED and DAED but as these substances are readily biodegraded under aerobic conditions and sorption to sludge is low it is not very likely that anaerobic biodegradation would be a major fate pathway (see also chapter bacterial toxicity).

4.1.1.2 Biodegradation in Sediment and Soil

Data on the aerobic and anaerobic degradability of TAED and DAED in sediment and soil are not available. Therefore it is assumed that the half-life of TAED and DAED in aerated sediment and soil will be double the half-life in surface water which is 2*9 d = **18 d**. This is in accordance to the EU Technical Guidance Document for Risk Assessments (EU, 1996) for low sorbing substances which assumes double the half-life in water for sediment and soil.

4.1.1.3 Abiotic Degradation in Air

Due to the low volatility of TAED and DAED and due to the fact that the emissions are directed to sewage degradation in air is not a relevant fate pathway and therefore not considered in this assessment.

4.1.1.4 Abiotic Degradation during the Washing Process

As mentioned already earlier TAED is converted rapidly into DAED under the strong alkaline conditions of the washing process and in presence of perborate or percarbonate (Gilbert, 1992; Buecking et al., 1990).

The perhydrolysis of TAED (Clariant, 2002a) under conditions similar to the washing process (perborate, sodium carbonate, sodium disilicate but without detergent which would interfere with the analytics) was carried out at room temperature (23 degree C) which is below the temperature recommended for washing powders containing TAED. The analytical results show that TAED is rapidly perhydrolysed and after about 20 min at room temperature only 1% is left in the solution. TriAED could be detected only during a short period and was below detection limit after 20 min. DAED was the final product and did not degrade further within the total reaction time of 120 min = 2h (see table 4.1.1.4 and 4.1.1.5).

Table 4.1.1.4 Perhydrolysis of TAED at room temperature (23 degree C) under alkaline conditions (pH=10.1) and presence of perborate

Time t (min)	TAED (Mol-%)	TriAED (Mol-%)	DAED (Mol-%)
0	100	-	-
5	32	5.5	58.4
10	7	1.8	112
20	1.4	< 0,2*	116
30	< 0,2*	< 0,2*	115
60	< 0,2*	< 0,2*	116
120	< 0,2*	< 0,2*	115

*** means below detection limit, values above 100 Mol-% reflect the uncertainty of the analytical determination**

The regression analysis of these kinetic data results in a pseudo first order kinetic (Clariant, 2002a) with

TAED $t_{1/2}$ = 3 min	at pH 10.1, 23 degree C, 0.5 g/l TAED, and 1.5 g/l Sodium perborate

4.1.1.5 Abiotic Degradation in Water

Photolysis in water can be neglected (see above) and therefore only hydrolysis is considered.

Hydrolysis

Under environmentally relevant conditions (e.g. pH=7, 15 degree C) TAED is rather resistant to hydrolysis (see table 4.1.1.5). The Syracuse Estimation Program HydroWIN predicts even longer half-lives (see table 4.1.1.5).

Clariant has recently investigated the hydrolysis of TAED under strongly alkaline conditions at pH=10 (Clariant, 2002a). Regression analysis of the kinetic data clearly shows that the hydrolysis does neither follow 1st nor 2nd order kinetic. This means that the first half-life derived from the regression curve and as given in Table 4.1.1.5 will decrease over time.

Table 4.1.1.5 Hydrolysis

Hydrolysis		Half-life $t_{1/2}$	Reliability	Remark / Reference
Unilver results at pH=7, 15 degree C	**TAED**	40 d	4	Gilbert, 1992
	DAED	Stable	4	AISE, 1992
Estimation of Hydrolysis by Syracuse HydroWin	**TAED**	>365 d	3	SRC HydroWin, 1999
	DAED	>365 d	4	SRC HydroWin, 1999
Clariant results at pH=10, 21 degree C	**TAED**	ca. 0.3 h	1	Clariant, 2002a; non-linear kinetic, first half-life only, half-life decreases over time
	DAED	?	-	no decrease in DAED concentration was observed during the hydrolysis study of TAED (observation period 17h)
Clariant results recalculated for pH=7, 21 degree C	**TAED**	ca. 13 d (first half-life only !)	1	Clariant, 2002a; non-linear kinetic, first half-life only, half-life decreases over time; 1000 times longer $t_{1/2}$ in comparison to pH 10

Reliability criteria of IUCLID are used:
1 valid without restriction 2 valid with restrictions 3 not valid 4 validity is not assignable

These results demonstrate that hydrolysis of TAED and DAED under environmental conditions is slow in comparison to biodegradation. Therefore, the hydrolysis of TAED and DAED was not taken into account for the exposure assessment.

4.1.1.6 Abiotic Degradation in Sediment and Soil

Photolysis in sediment and soil is not relevant (see above). Hydrolysis of TAED and DAED can occur in the interstitial water of the sediment or the pore water of soil but is most likely slow in comparison to biodegradation.

4.1.1.7 Volatilisation

TAED and DAED are highly water soluble and have a very low vapour pressure. The corresponding Henry coefficients (see table 3.1.2) are so low that volatilisation is not likely.

4.1.1.8 Sorption

Measured and estimated K_{oc} values (see table 3.1.2 & 4.1.1.6) and also the estimated K values from EUSES (see table 4.1.1.8) are so low that sorption is not a major removal process.

Table 4.1.1.8 Measured and estimated sorption coefficients

Sorption coefficients		Value (l/kg)	Reliability	Remark / Reference
K_{oc} (measured)	**TAED**	15 43-80	4 2	AISE, 1992 Shell, 2000 (different soils)
	DAED	25	4	AISE, 1992
K_{oc} (estimated SRC)	**TAED**	415	3	SRC PCKOC, 1999
	DAED	16	2	SRC PCKOC, 1999
Koc (estimated EUSES)	**TAED**	0.04	4	EUSES, 1997, reliability unclear
	DAED	0.11	4	EUSES, 1997, reliability unclear

Reliability criteria of IUCLID are used:
1 valid without restriction 2 valid with restrictions 3 not valid 4 validity is not assignable

4.1.1.9 Bioconcentration

Due to the high water solubility and negative octanol-water partitioning coefficients TAED, and DAED have no significant tendency to bioaccumulate. BCF values (see table 4.1.1.9) were calculated with the estimation program Syracuse BCF (SRC BCF, 1999).

Table 4.1.1.9 Bioconcentration

Bioconcentration		BCF	Reliability	Remark / Reference
Bioconcentration in fish	**TAED**	3.2	2	SRC BCF, 1999
	DAED	3.2	2	SRC BCF, 1999

Reliability criteria of IUCLID are used:
1 valid without restriction 2 valid with restrictions 3 not valid 4 validity is not assignable

4.1.2 Removal

Removal in Sewage Treatment Plants (STPs)

Based on the data in chapter 4.1.1 (table 4.1.1.1) at least 97% of TAED and DAED is eliminated in the STP. As the sorption tendency of TAED and DAED to sewage sludge is low as well (see table 4.1.1.6) only about 0.1% (calculated by the wwtp model within EUSES) is transfered to sludge and about 3% is released to surface water via effluent (details see EUSES calculations of PEC; EUSES TAED/DAED, 2002).

4.1.3 Monitoring studies

Monitoring data are not available.

4.1.4 PEC Calculations

4.1.4.1 Releases

More than 99% of the TAED it is converted during the washing process into DAED (see chapter 4.1.1). In this exposure assessment it is assumed that the waste water from the washing process contains 1 Mol-% TAED and 99Mol-% DAED. It is important to note that the molweight of DAED (M = 144.17 g/Mol) is only 63% of the molweight of TAED (M = 228.25 g/Mol; see chapter 3.1). This means 99 Mol-% DAED corresponds to 62 Mass-% TAED. Direct releases to air are not relevant and assumed to be zero.
Table 4.1.4.1 shows the total tonnage of TAED consumed (AISE, 2002) as well as the tonnage of TAED and DAED released to the sewer during the washing process.

Table 4.1.4.1 Tonnage of TEAD used and released tonnage of TAED and DAED

Tonnages used		No.	tons/year	Remark/Reference
Total tonnage consumed in EU	**TAED**	[1]	**61000**	AISE, 2002
	DAED		-	-
Total tonnage released to EU sewer	**TAED**	[2]	**610**	[2] = [1] * 0,01
	DAED	[3]	**38046**	[3] = [1] * 0,99 * 0,63 (0,63 corrects lower MW)

PEC calculations are using two release scenarios. One is the EUSES Default scenario according TGD (EU, 1996; Industry category 5: Personal & domestic use, Use category 9: Cleaning/washing agents and additives), the other is a modification of the latter according to the HERA Guidance Document (HERA, 2001).

4.1.4.2 Aquatic Compartment

Table 4.1.4.2 $c_{local, water}$ and PEC_{water} for TAED and DAED

Water compartment					
	No.		**Scenario EUSES**	**Scenario HERA**	**Remark**
$c_{local, water}$ (µg/l)	[14]	**TAED**	**0,5**	**0,08**	
	[15]	**DAED**	**31,2**	**8,2**	
$PEC_{regional, water}$ (µg/l)	[16]	**TAED**	**0,09**	**0,06**	
	[17]	**DAED**	**6,5**	**4,6**	
$PEC_{local, water}$ (µg/l)	[18]	**TAED**	**0,59**	**0,15**	[18] = [14] + [16]
	[19]	**DAED**	**37,7**	**12,8**	[19] = [15] + [17]

As can be seen from table 4.1.4.2 the local concentrations of the scenario EUSES and HERA differ by a factor up to 4. The differences between the regional concentrations are less pronounced as the difference for the mass loading differs not much (10% versus 7% of total consumption figure).

4.1.4.3 Sediment Compartment

Table 4.1.4.3 $c_{local, sediment}$ and $PEC_{sediment}$ for TAED and DAED

Sediment compartment					
	No.		**Scenario EUSES**	**Scenario HERA**	**Remark**
$c_{local, sediment}$ (µg/kg dw)	[20]	**TAED**	**1,50**	**0,26**	
	[21]	**DAED**	**113**	**31,9**	
$PEC_{regional, sediment}$ (µg/kg dw)	[22]	**TAED**	**0,20**	**0,14**	
	[23]	**DAED**	**17,3**	**12,2**	
$PEC_{local, sediment}$ (µg/kg dw)	[24]	**TAED**	**1,70**	**0,4**	[24] = [20] + [22]
	[25]	**DAED**	**130**	**44,1**	[25] = [21] + [23]

Here again the differences in the local concentrations can be seen between the two release scenarios which is caused by the different main local sources.

4.1.4.4 Soil Compartment

Due to the low sorption tendency of TAED and DAED one would assume to find low sludge concentrations. But due to the high consumption rate of TAED the concentrations in wet sludge expressed as dry weight (dw) are in the mg/l-range in sludge and in the µg/l-range in soil for DAED. The different soil concentrations are used for different risk endpoints (see table 4.1.4.4).

Table 4.1.4.4 $c_{local, soil}$ and PEC_{soil} for TAED and DAED

Soil compartment					
	No.		**Scenario EUSES**	**Scenario HERA**	**Remark**
$c_{local, sludge}$ (µg/kg dw)	[26]	**TAED**	**600**	**100**	
	[27]	**DAED**	**62000**	**16300**	
$c_{local, soil}$ (µg/kg dw)	[28]	**TAED**	**0,6**	**0,09**	**30d average**
	[29]	**DAED**	**59,5**	**15,6**	**30d average**
$c_{local, agric. soil}$ (µg/kg dw)	[30]	**TAED**	**0,13**	**0,02**	**180 d average**
	[31]	**DAED**	**14,0**	**3,7**	**180 d average**
$c_{local, grassland}$ (µg/kg dw)	[32]	**TAED**	**0,05**	**0,008**	
	[33]	**DAED**	**5,3**	**1,4**	
$PEC_{regional, natural soil}$ (µg/kg dw)	[34]	**TAED**	**4*E-08**	**2,9*E-08**	
	[35]	**DAED**	**2,3*E-07**	**1,6*E-07**	
$PEC_{local, soil}$ (µg/kg dw) (endpoint terrestr. ecosystem)	[36]	**TAED**	**0,6**	**0,09**	[36] = [28] + [34]
	[37]	**DAED**	**59,5**	**15,6**	[37] = [29] + [35]
$PEC_{local, agric. soil}$ (µg/kg dw) (endpoint crops for human)	[38]	**TAED**	**0,13**	**0,02**	[38] = [30] + [34]
	[39]	**DAED**	**14,0**	**3,7**	[39] = [31] + [35]
$PEC_{local, grassland}$ (µg/kg dw) (endpoint grass for cattle)	[40]	**TAED**	**0,05**	**0,008**	[40] = [32] + [34]
	[41]	**DAED**	**5,3**	**1,4**	[41] = [33] + [35]

The differences in local concentrations between the two scenarios EUSES and HERA are caused again by the different main local sources.

4.1.4.5 Sewage Treatment Plant (STP)

As TAED is used continuously (365 d/a) the effluent concentration of the sewage treatment plant is equivalent to the PECstp.

Table 4.1.4.5 PEC_{stp} for TAED and DAED

Sewage treatment plant (stp)					
	No.		**Scenario EUSES**	**Scenario HERA**	**Remark**
PEC_{stp} (µg/l)	[42]	**TAED**	**5,0**	**0,83**	
	[43]	**DAED**	**312**	**82**	

4.1.4.6 Secondary Poisoning

As the BCFs of TAED and DAED are very low secondary poisoning is unlikely and therefore not covered in this assessment.

4.1.4.7 Indirect Exposure of Humans via Environment

From environmental concentrations and transfer factors EUSES calculates local and regional concentrations in food (vegetables, meat, milk etc), air and drinking water. The daily intakes estimated are highly uncertain as the log Kow of TAED and DAED are most likely out of the domain of the equations used to calculate the transfer between the different media. Nevertheless it can be concluded from these estimates that indirect exposure of humans via the environment is very low and therefore need not to be taken into account in the human health exposure assessment.

4.2. Environmental Effects Assessment

In the following the available ecotoxicity data of TAED and DAED are listed.

4.2.1 Ecotoxicity

4.2.1.1 Aquatic Ecotoxicty

Acute Aquatic Ecotoxicity

TAED and DAED have a low acute ecotoxicity profile (see table 4.2.1.1.1). For all ecotoxicity studies on fish, daphnia and algae the L(E)C50 is above the highest tested concentration.

Toxicity to aerobic and anaerobic bacteria is low as well.

Chronic Ecotoxicity

Only one chronic study is available. It is an Algae 14d Growth Inhibition Test (see table 4.2.1.1.2)

4.2.1.2 Sediment and Soil Ecotoxicty

No data on sediment or soil ecotoxicity of TAED and DAED are available.

Table 4.2.1.1.1 Acute Aquatic Ecotoxicity

Acute Fish Toxicity						
Species	**Substance**	**Guideline**	**Exposure (h)**	**LC50 (mg/l)**	**Reliability**	**Remark / Reference**
Carrasius auratus	TAED	DIN 38412 part 15	24	> 250	4	Reinhardt et al, 1989
		Unilever	24	> 2500	2	Unilever, 1979
		?	24	> 30000	4	Schoeberl et al, 1988
		Unilever	96	> 1600	2	Unilever, 1979
		?	96	> 2500	4	no effects at highest conc. tested;Schoeberl et al, 1988
	DAED	?	96	40000-75000	4	Gilbert, 1992
Danio rerio	TAED	OECD 203	96	> 500	2	Hoechst, 1985
		?	96	> 1500	4	no effects at highest conc. tested; Gilbert, 1992, Procter & Gamble, 2002
	DAED	-	-	-	-	-
Leuciscus idus	TAED	?	48	> 200	4	no effects at highest conc. tested; Gilbert, 1992, Procter & Gamble, 2002
		DIN 38412, part 15	48	> 250	2	Henkel, 1972d
	DAED	DIN 38412, part 15 ?	48 48	> 250 > 200	2 4	Henkel, 1972e Procter & Gamble, 2002
Oncorhynchus mykiss	TAED	OPPTS 850.1075	96	140 (NOEC)	1	Warwick, 2000b

Reliability criteria of IUCLID are used:
1 valid without restriction 2 valid with restrictions 3 not valid 4 validity is not assignable

Table 4.2.1.1.1 Acute Aquatic Ecotoxicity (continued)

Acute Toxcitiy to Aquatic Invertebrates						
Species	**Substance**	**Guideline**	**Exposure (h)**	**EC50 (mg/l)**	**Reliability**	**Remark / Reference**
Daphnia magna	**TAED**	DIN 38412, part 11	24	> 500	2	Henkel, 1972f
		?	24	1600	4	Procter & Gamble, 2002
		Unilever	48	> 800	2	insufficient effects for calc. of EC50; Unilever, 1979
		?	48	963	4	Procter & Gamble, 2002
	DAED	?	48	> 800	4	insufficient effects for calc. of EC50; Gilbert, 1992
		DIN 38412, part 11	24	> 500	2	Henkel, 1972g
Gammarus pulex	**TAED**	Unilever	72	> 800	2	no effects at highest conc.; Unilever, 1979
	DAED	?	72	> 800	4	no effects at highest conc.; Gilbert, 1992
Acute Toxcitiy to Algae						
Species	**Substance**	**Guideline**	**Exposure (d)**	**EC50 (mg/l)**	**Reliability**	**Remark / Reference**
Chlorella vulgaris	**TAED**	Unilever	14	> 500	2	no effects on growth at highest conc.; Unilever, 1979
	DAED	?	14	> 500	4	no effects on growth at highest conc.; Gilbert, 1992

Reliability criteria of IUCLID are used:
1 valid without restriction 2 valid with restrictions 3 not valid 4 validity is not assignable

Table 4.2.1.1.1 Acute Aquatic Ecotoxicity (continued)

Acute Toxcity to Aerobic Bacteria						
Species	**Substance**	**Guideline**	**Exposure (h)**	**EC50 (mg/l)**	**Reliability**	**Remark / Reference**
Domestic Sewage Sludge	**TAED**	OECD 209	24	> 1000	2	Hoechst, 1992
Acute Toxcity to Anaerobic Bacteria						
Species	**Substance**	**Guideline**	**Exposure (h)**	**EC0 (mg/l)**	**Reliability**	**Remark / Reference**
Anaerobic bacteria from domestic stp	**TAED**	ETA Fermentation Tube Method	24	3000	2	Hoechst, 1970
Anaerobic bacteria from digester	**TAED**				4	up to 80 g TAED/kg dry digester solid has no effect on gas production; Gilbert, 1992
	DAED				4	no effect up to 80g DAED/kg dw., Gilbert, 1992

Reliability criteria of IUCLID are used:
1 valid without restriction 2 valid with restrictions 3 not valid 4 validity is not assignable

Table 4.2.1.1.2 Chronic Aquatic Ecotoxicity

Chronic Toxcitiy to Algae						
Species	**Substance**	**Guideline**	**Exposure (d)**	**NOEC (mg/l)**	**Reliability**	**Remark / Reference**
Chlorella vulgaris	**TAED**	Unilever	14	> 500	2	no effects on growth at highest conc.; Gilbert, 1992
	DAED	?	14	> 500	4	no effects on growth at highest conc.; Gilbert, 1992

Reliability criteria of IUCLID are used:
1 valid without restriction 2 valid with restrictions 3 not valid 4 validity is not assignable

4.2.2 PNEC Calculations

General

The PNECs derived in the following are summarized in table 4.2.2.1.

4.2.2.1 $PNEC_{water}$

Due to the low aquatic toxicity of TAED and DAED, no toxic effects were observed in most acute studies, hence no L(E)C50 values could be derived which would be necessary to derive the $PNEC_{water}$ as described in the EU Technical Guidance Document for Risk Assessments (EU, 1996). As only one chronic NOEC is available (algae) this is not an alternative to derive the $PNEC_{water}$.

Based on all available data on aquatic organisms (see chapter 4.2.1 and tables therein) it can be assumed conservatively that the lowest acute aquatic L(E)C50 is 500 mg/l for TAED and DAED (half of the water solubility). Using an application factor of 1000 according to TGD (EU, 1996) a **$PNEC_{water}$** of **500 µg/l** can be calculated.

4.2.2.2 $PNEC_{sediment}$

As no sediment ecotoxicity studies are available the equilibrium partitioning method described in the EU TGD was used (EU, 1996) to derive the $PNEC_{sediment}$ with help of EUSES. No extra application factor was applied because TAED and DAED show low sorptivity. Based on the assumed lowest aquatic L(E)C50 of 500 mg/l a **$PNEC_{sediment}$** of **1,18 mg/kg dw.** for TAED and DAED was calculated.

4.2.2.3 $PNEC_{soil}$

As no soil ecotoxicity studies are availble the equilibrium partitioning method described in the EU TGD was used (EU, 1996) to derive the $PNEC_{soil}$ with help of EUSES. No extra application factor was applied because TAED and DAED show low sorptivity. Based on the assumed lowest aquatic L(E)C50 of 500 mg/l a **$PNEC_{soil}$** of **220 µg/kg dw.** for TAED and DAED was calculated.

4.2.2.4 $PNEC_{stp}$

For TAED it is assumed that the EC50 for bacteria is 1000 mg/l (see table 4.2.1.1.1) and for DAED that the bacterial toxicity is similar to TAED. The latter assumption is justified considering the good comparability of the aquatic toxicity of both compounds. The **$PNEC_{stp}$** of **10 mg/l** for TAED and DAED is derived from the TAED result 1000 mg/l using an application factor of 100.

Summary of the PNECS for TAED and DAED

Table 4.2.2.1 PNECs for TAED and DAED

PNECs for TAED and DAED		
	Value	**Remark**
$PNEC_{water}$ (µg/l)	**500**	assumed L(E)C50 500 mg/l, application factor 1000
$PNEC_{sediment}$ (mg/kg dw.)	**1,18**	equilibrium partitioning method using assumed aquatic L(E)C50, no extra application factor
$PNEC_{soil}$ (mg/kg dw.)	**0,22**	equilibrium partitioning method using assumed aquatic L(E)C50, no extra application factor
$PNEC_{stp}$ (mg/l)	**10**	derived from acute bacteria study, application factor 100

4.3. Environmental Risk Characterisation

In the following the Risk Characterisation for the relevant Envrionmental Compartments (surface water, sediment, soil and stp) are calculated from the PECs given in chapter 4.1.4 and the PNECs derived in chapter 4.2.2. The PEC/PNECs are summarized in Table 4.3.

Table 4.3 Environmental Risk Characterisation for TAED and DAED

Risk Charcterisation Aquatic compartment				
		Scenario EUSES	**Scenario HERA**	**Remark**
$PEC_{local, water}/PNEC_{water}$	**TAED**	**1,2*E-03**	**2,9*E-04**	based on acute data
	DAED	**7,5*E-02**	**2,6*E-02**	based on acute data
Risk Characterisation Sediment compartment				
		Scenario EUSES	**Scenario HERA**	**Remark**
$PEC_{local, sediment}/PNEC_{sed.}$	**TAED**	**1,5*E-03**	**3,6*E-04**	equilib. partitioning method used
	DAED	**9,1*E-02**	**3,1*E-02**	equilib. partitioning method used
Risk Characterisation Soil compartment				
		Scenario EUSES	**Scenario HERA**	**Remark**
$PEC_{local, soil}/PNEC_{soil}$	**TAED**	**2,6*E-03**	**4,3*E-04**	equilib. partitioning method used
	DAED	**1,9*E-01**	**4,9*E-02**	equilib. partitioning method used
Risk Charaterisation Sewage Treatment Plant				
		Scenario EUSES	**Scenario HERA**	**Remark**
PEC_{stp} /$PNEC_{stp}$	**TAED**	**5*E-04**	**8,3*E-05**	-
	DAED	**3,1*E-02**	**8,2*E-03**	$PNEC_{stp}$ is based on TAED data

4.4 Discussion and Conclusions

As shown in chapter 4.3, the Risk Characterisation Ratio (RCR) for TAED and DEAD is < 1 in all environmental compartments which may be potentially affected by the exposure to these substances (water, sediment, soil, sewage treatment plants). It should be pointed out in this context that very conservative assumptions were made in the derivation of $PNEC_{aquatic}$ in order to compensate for the limited suitability of some of the ecotoxicological data for obtaining clear-cut effect concentrations.

For water, the PNEC derived from the acute aquatic toxicity data is likely to be very conservative as the available EC/LC50 values indicate that the acute aquatic effect concentration for TAED and DAED is above the highest tested concentration or above water solubility (see 4.2.1.1). Except for the algae NOEC, no chronic data for TAED and DAED in the aquatic compartment are available. However, these chronic data also give no indication of a significant long-term toxicity of these compounds.

Taking into account the resulting HERA RCR of < 0.1 it does it is not necessary to improve the present risk characterisation with help of new additional ecotoxicity data.

The same conclusion can be drawn for the sediments compartment. The PNEC value used for this part of the risk characterisation is based on the aquatic toxicity data and has been derived for the sediments according to the TGD using the equilibrium partitioning approach. Therefore, the conservative nature of the aquatic toxicity data used and the resulting HERA RCR of < 0.1 may be considered as a sufficient justification to conclude that there is no need for additional data specifically addressing the sediments compartment.

Both of the two exposure scenarios for TAED and DAED in the soil compartment (EUSES and HERA scenario) result in a RCR of < 1 indicating no risk in spite of the conservative nature of these exposure scenarios and of the underlying effect concentrations as well which were derived again from the aquatic toxicity data according to the TGD using the equilibrium partitioning approach.

5. Human Health Assessment

5.1 Initial Remarks

TAED is a bleaching activator which is mainly used in detergents and additives for laundry washing and dishwashing. After starting the washing process, TAED is completely dissolved within minutes in the wash liquor and undergoes perhydrolysis in the presence of persalts such as perborate or percarbonate via triacetylethylenediamine (TriAED) to diacetylethylene-diamine (DAED) and to peracetic acid, which provides efficient bleaching and hygiene benefits at low washing temperatures. Detergents contain an excess of persalt ensuring a degree of TAED perhydrolysis >99% even at room temperature (Hirschen & Meuth, 2002). The solubility of TAED in water increases with rising temperatures, being 2 g/l at 20°C, 5 g/l at 40°C and 10 g/l at 60°C. These values are far above the maximum concentration of the activator used in detergents (normally 0.1-0.5 g/l washing liquor) (Gilbert, 1992, Clariant, 1999). The water solubility of DAED is >1000 g/l at room temperature (Clariant, 2002). TAED is used only in granulated form to increase storage stability. Particles with a size below 0.2 mm amount to less than 3% (Clariant, 1999).
The present assessment takes into account the parent compound TAED as well as the final degradation product DAED. TriAED is not assessed in this report as no significant concentrations arise during the perhydrolysis process (Hirschen & Meuth, 2002). Also, peracetic acid is not assessed as it is not a perhydrolysis product of TAED itself and moreover, an assessment has already been published (ECETOC, 2001).

5.2 Consumer Exposure

5.2.1 Product Types

TAED is used in heavy duty washing and machine dishwashing powders and tablets as well as in bleach boosters. The TAED concentration in the various products depends on the type of product and ranges between 0.4 and 13% (table 1, AISE, 2002a).

Table 1. Content of TAED in consumer products (AISE, 2002a).

Product Type	%TAED in Product		
	Min	Max	Typical Range
Regular heavy duty powder	0.4	3.4	1.4-2.5
Compact heavy duty powder	1.0	7.0	3.0-6.0
Compact heavy duty tablets	1.5	7.0	2.0-6.0
Powder bleach	1.2	8.7	4.0-7.2
Tablet bleach	7.0	13.0	13.0
Machine dishwashing powder	0.9	3.0	1.4-2.5
Machine dishwashing tablets	0.5	3.2	2.5

Other product types containing TAED, such as denture cleaners for example, are not in the focus of this HERA risk assessment. Products solely used for hand washing or pretreatment of fabrics or hand dishwashing do not contain TAED.

5.2.2 Consumer Contact Scenarios

Based on the product types the following relevant consumer contact scenarios can be anticipated:

1) Dermal contact
   a) Contact with clothes containing deposited product
   b) Direct dermal contact
2) Contact via inhalation

   Pouring the product from the container into the machine
3) Oral ingestion
   a) Ingestion of product residues on eating utensils and dishes
   b) Indirect exposure via the environment
   c) Accidental over exposure or intentional misuse
4) Accidental eye contact with products

5.2.3 Consumer Exposure Estimates

5.2.3.1 Initial Remarks

To estimate the amount of TAED and DAED to which consumers are exposed the following was defined:

- the perhydrolysis of TAED yields 1% TAED and 99% DAED
- the maximum concentration of TAED in consumer products given in table 1 is taken for exposure estimation
- the maximum values depicted in 'Table of habits and practices for consumer products in Western Europe' are used for a) the amount of product used per task and b) the number of tasks per week (AISE, 2002b).

Using the maximum values as indicated above leads to worst case scenarios which overestimate the exposure for most of the consumers.

5.2.3.2 Dermal Exposure

5.2.3.2.1Contact with clothes containing deposited product

Residues of laundry detergent ingredients may remain on clothes after washing and may be transferred to skin. The maximum amount of TAED used for laundry results from the use of powder bleach (70 g containing 8.7% TAED) in addition to a compact heavy duty detergent (200 g containing 7% TAED) and amounts to 20.09 g TAED/wash.
After the perhydrolysis of TAED, 0.20 g TAED and 12.56 g DAED are present in the washing liquor. The concentration of a water soluble ingredient of a detergent is decreased to less than 2.5% of the initial concentration in the wash-liquor before final spinning (ZVEI and IKW, 1999), thus, leading to a maximum of 0.34 mg/l and 20.9 mg/l of TAED and DAED, respectively, assuming 15 l of washing liquor. After final spinning using 1000 rpm a wash load of mixed fabrics contains approximately 60% liquor (Henkel, 2002a). Taking into account a fabric density of 20 mg/cm^2 (Henkel, 2002b), the TAED and DAED load deposited on fabrics equals 4.02 x 10^{-6} and 2.51 x 10^{-4} mg/cm^2 fabric, respectively.
The systemic exposure to TAED and DAED is estimated according to the following algorithm given in the HERA Guidance Document (2002):

$$\boldsymbol{Exp_{sys}(TAED) = F_1 \times C'_{TAED} \times S_{der} \times n \times F_2 \times F_3 \times F_4 / BW = 5.07 \times 10^{-7}\ mg/kg\ BW/d}$$
$$\boldsymbol{Exp_{sys}(DAED) = F_1 \times C'_{DAED} \times S_{der} \times n \times F_2 \times F_3 \times F_4 / BW = 3.17 \times 10^{-5}\ mg/kg\ BW/d}$$

The terms are defined with the following values:

F_1 (weight fraction of substance in product; not used, already included in C')

$C`_{TAED}$ = 4.02 x $10^{-6}$ mg/cm$^2$, $C`_{DAED}$ = 2.51 x 10^{-4} mg/cm^2 (product load)

S_{der} = 17600 cm^2 (surface area of total body excluding hands and head (TGD, 1996))

n = 1 (product use frequency in number [events/day])

F_2 = 0.01 (weight fraction transferred from medium to skin (Vermeire et al., 1993))

F_3 = 1 (weight fraction remaining on skin; worst case assumption)

$F_{4(TAED)} = F_{4(DAED)}$ = 0.043 (weight fraction absorbed via skin; the value is taken from the TAED skin penetration study described in 5.3.1.8.2 and represents the amounts of TAED penetrating skin within two days after application; for DAED the same value is used, as the physical chemical properties of DAED and TAED are very similar and hence, a comparable skin penetration can be assumed)

BW = 60 kg (body weight)

5.2.3.2.2 Direct skin contact with tablets or powder

Contact with laundry, bleach booster and dishwashing tablets occurs frequently during unwrapping the tablets and placing them into the washing or dishwashing machine. However, contact time is very low (<1 min) and only the tips of thumb and index finger of one hand are exposed (appr. 2 cm^2 skin) so that the amount absorbed percutaneously can be neglected.

Some parts of the body, mainly the hand, might also come in contact with washing, bleach booster or dishwashing powder when transferring the product from the container into the machine or accidentally spilling some powder. Contact time during these scenarios is very low (< 1min), the skin area affected is small (usually much less than the area of one hand (420 cm^2)) and exposure occurs only occasionally and not regularly with product use. Hence, the systemic TAED exposure resulting from this scenario is also considered to be negligible.

5.2.3.2.3 Direct skin contact via hand-washed laundry

Using machine-washing detergents for handwashing results in direct contact of hands and forearms with detergent solutions. According to AISE (2002b) a hand-wash takes a maximum of 10 min and the highest concentration of detergent used in the wash solution is 1%. This corresponds to 0.07% or 0.7 g TAED/l wash solution when using a compact heavy duty powder as a worst case assumption.

The skin is not only exposed to TAED but also to TriAED and DAED, as almost complete perhydrolyzation of TAED takes place during a 10 min hand-wash (Hirschen and Meuth, 2002). Exposure to TriAED can be neglected since TriAED is very rapidly converted to DAED as soon as it is formed (Martin Davies and Deary, 1991; Hirschen and Meuth, 2002). For the sake of simplicity it is assumed, that the skin is exposed to both the initial concentration of TAED and the maximum concentration of DAED (= 0.44 mg/ml, assuming a 99% TAED perhydrolysis) during the whole wash-process of 10 min.

According to the algorithm given in the HERA Guidance Document (2002)the following exposure can be derived for a 10 min hand-wash:

$$\boldsymbol{Exp_{sys}(TAED)} = F_1 \times C'_{TAED} \times S_{der} \times n \times F_2 \times F_4 / BW = 1.65 \times 10^{-3} \text{ mg/kg BW/d}$$
$$\boldsymbol{= 1.15 \times 10^{-5} \text{ mg/kg BW/10 min}}$$
$$\boldsymbol{Exp_{sys}(DAED)} = F_1 \times C'_{DAED} \times S_{der} \times n \times F_2 \times F_4 / BW = 1.04 \times 10^{-3} \text{ mg/kg BW/d}$$
$$\boldsymbol{= 7.22 \times 10^{-6} \text{ mg/kg BW/10 min}}$$

The terms are defined with the following values:

F_1 (weight fraction of substance in product; not used, already included in C')

$C`_{TAED}$ = 0.7 mg/ml, $C`_{DAED}$ = 0.44 mg/ml (substance concentration in liquor)

S_{der} = 1980 cm^2 (surface area of hands and forearms (TGD, 1996))

n = 0.714 (product use frequency in number [events/day]; the maximum number of product uses per week given by AISE (2002b) is 21, as there is no differentiation between hand- and machine-wash, 5 hand-washes/week are assumed as worst case)

F_2 = 0.01 cm (film thickness (Vermeire et al., 1993))

$F_{4(TAED)} = F_{4(DAED)}$ = 0.01 (weight fraction absorbed via skin; the value is taken from the TAED skin penetration study described in 5.3.1.8.2 and represents the amounts of TAED penetrating skin within two days after a 10 min dermal exposure; for DAED the same value is used, as the physical chemical properties of DAED and TAED are

very similar and hence, a comparable skin penetration can be assumed)

BW = 60 kg (body weight)

5.2.3.3 Inhalation Exposure

Van den Plassche et al. (1999) have estimated that pouring and use of one cup powdered laundry detergent (200 g) can generate 0.27 µg dust. As mentioned above, TAED is used only in a granulated form. The amount of particles with a diameter <0.2 mm is less than 3%. Taking into account a TAED concentration of 7% when using 200 g of a compact heavy duty powder and assuming that all particles with a size below 0.2 mm are so small that they can be inhaled, the inhalable TAED dust generated by pouring a cup of powder amounts to 5.7×10^{-7} mg/use. Even assuming that this amount is completely inhaled and bioavailable – which is a gross exaggeration – the systemic TAED exposure would be only 9.5×10^{-9} mg/kg BW/use or 2.85×10^{-8} mg/kg BW/d assuming 21 uses/week. This exposure may be considered insignificant.

Lint formation during drying fabrics in tumble-dryers does not constitute appreciable inhalation exposure, since washed fabrics contain only very little DAED and TAED (see 5.2.3.2.1).

5.2.3.4 Oral Ingestion

5.2.3.4.1 Residues on dishes and eating utensils

Machine dishwashing powder and tablets contain up to 3.2% TAED. Hence, residues of TAED and DAED may remain on dishes and eating utensils after cleaning and may be ingested upon migration into food and drink.

According to AISE (2002) the maximum amount of detergent used per wash is 50 g. A typical dishwashing program consists of three to four wash-cycles using approximately 4.3 l water each. After each wash-cycle the washing liquor is pumped off and only 0.2-0.3 l remain (Bauknecht GmbH, 2002).

Based on the data given above the initial TAED concentration is 372 mg/l which leads to 3.72 mg/l TAED and 232.6 mg/l DAED after perhydrolysis. These substance concentrations are decreased to 0.015 mg TAED/l and 1.0 mg DAED/l assuming three wash-cycles during which 0.3 l is left after pumping off the washing liquor and 4.3 l of fresh water are newly added.

0.55 µl liquor remain on a surface of 1 cm^2 at the end of the wash process (Official publication French legislation, 1990). Thus, a TAED and DAED load of 8.3 x 10^{-9} mg/cm^2 and 5.5 x 10^{-7} mg/cm^2, respectively, can be calculated.
The systemic oral exposure can then be determined according to the following algorithm (HERA Guidance Document 2002):

$$\boldsymbol{Exp_{sys}(TAED) = F_1 \times C'_{TAED} \times S \times F'' \times F_9 / BW = 7.5 \times 10^{-7}\ mg/kg\ BW/d}$$
$$\boldsymbol{Exp_{sys}(DAED) = F_1 \times C'_{DAED} \times S \times F'' \times F_9 / BW = 5.0 \times 10^{-5}\ mg/kg\ BW/d}$$

The terms are defined with the following values:

F1 (weight fraction of substance in product; not used, already included in *C'*)

C'_{TAED} = 8.3 x 10^{-9} mg/cm^2, C'_{DAED} = 5.5 x 10^{-7} mg/cm^2 (substance load)

S = 5400 cm^2 (surface area of dishes/eating utensils used per day (Official publication French legislation, 1990)

F'' = 1 (weight fraction of substance transferred from article and ingested; it is assumed that all of the substance present on the article is transferred to food or drink and ingested)

F_9 = 1 (weight fraction absorbed or bioavailability; value taken from biokinetics study described in 5.3.1.8.1)

BW = 60 kg

5.2.3.4.2 Mouthing and sucking on fabrics

Babies and young children may mouth or suck on fabrics containing up to 4.02 x 10^{-6} mg TEAD/cm^2 and 2.51 x 10^{-4} mg DAED/cm^2 fabric (see 5.2.3.2.1). Due to this very low substance load and the fact that mouthing/sucking occurs only over a very limited time period on a small area of fabric the exposure resulting from this scenario may be considered insignificant.

5.2.3.4.3 Contaminated food and drinking water

In the environmental assessment (4.1.4.7) it was concluded that indirect exposure arising from consumption of contaminated drinking water is so low that it has not to be taken into account. Hence, this exposure scenario may be considered insignificant.

5.2.3.4.4 Accidental ingestion or intentional overexposure

Accidental ingestion or intentional over exposure are assumed as rare events. However, especially young children of crawling to toddler age might accidentally ingest TAED containing products. About 5 g of a powder product will probably be all that can be ingested. The body weight can be as low as 10 kg. Based on the highest TAED content of 8.7% present in bleach boosters, the maximum accidental oral TAED dose is considered to be 44 mg/kg BW/event.

Accidental ingestion of DAED can only occur when drinking some wash solution. However, the concentration of DAED in the wash solution as well as the amount ingested will be so small that no concern arises.

5.2.3.5 Eye Contact

Accidental spillage may result in eye contact with TAED containing products.

5.3 Hazard Assessment

5.3.1 Summary of the Available Toxicological Data

In the following data quality has been assigned according to the criteria defined by Klimisch et al. (1997) as outlined in the HERA Guidance Document (2002).

5.3.1.1 Acute Toxicity

5.3.1.1.1 Acute Oral Toxicity

The studies reporting the acute oral toxicity of **TAED** are summarized in table 2. Overall, the acute oral toxicity of TAED is very low.

In rats mortality did not occur up to doses of 2 g/kg BW. Reported LD50 values range between 7.94 and 10 g/kg BW. At 2 g/kg BW major symptoms of toxicity consisted of subdued activity, laboured respiration, hunched appearance and ataxia. At higher concentrations these symptoms became more severe and in addition spasms, pilar erection, closed eyes and weight loss were observed. Gross necropsy was performed 14 days after treatment. The male and female survivor dosed of the 10 g/kg BW group which were necropsied showed slight thickening of the cardiac region, of the stomach wall and pale and patchy liver. All animals of the lower dose groups revealed no macroscopic lesions (Safepharm, 1982a).

In mice the acute oral LD50 value was 5.9 g/kg BW. No abnormalities were seen after dosing and at autopsy following a 21 day observation time.

Table 2. Acute Oral (Gavage) Toxicity of TAED.

Species	Animal Number per Dose Group	Test Material	LD50 in g/kg BW (95% con-fidence interval)	Data Quality Score[1)]	Reference
Rat	5 m, 5 f	pure	>2.0	1	HMR, 1999
	5 m, 5 f	90% TAED + 10% tallow alkyl ethoxylate	>2.0	1	Hoechst, 1986a
	5 m, 5 f	pure	7.94 (6.46-9.77)	1	Safepharm, 1982a
	10 m	pure	8.05 (6.44-10.06)	2	Henkel, 1980a
	3 m, 3 f	pure	>10	2[2)]	Unilever, 1976
mouse	3 m, 3 f	pure	5.9 (5.2-6.75)	2[2)]	Unilever, 1968

[1)] 1 = reliable without restrictions, performed according to GLP and OECD guideline 401
2 = reliable study, meeting many but not all requirements of OECD Guideline 401 and performed prior to GLP

[2)] Data quality was assigned by G. Moran (2002) of Unilever

The acute oral toxicity of **DAED** was determined according to OECD guideline 401 and GLP (data quality score 1, Toxikon Corporation, 2000a). 5 male and 5 female Sprague-Dawley rats received a single oral dose of 2 g/kg BW by gavage. The animals were killed and gross necropsy was performed after an observation period of 14 days. No animal died. There were no adverse clinical signs noted and no unusual lesions observed at necropsy. Based on these results DAED was defined as non-toxic by the authors.

5.3.1.1.2 Acute Inhalation Toxicity

Groups of 5 male and 5 female rats were exposed in inhalation chambers to 3.8, 25.4, 118.4 and 264.0 mg/m^3 **TAED** dust (< 3.5 µm) for 4 h (Unilever, 1980). All animals survived the exposure and the subsequent 14 day observation period. The main findings were systemic effects of increased relative liver weights and hepatic morphological changes, primarily in the highest concentration exposure group and particularly in the male rats. No histopathology changes related to TAED were found in the respiratory tract. The study is valid without restrictions (data quality score 1, assigned by G. Moran (2002) of Unilever).
There is no study available on **DAED**.

5.3.1.1.3 Acute Dermal Toxicity

No studies have been identified describing the acute dermal toxicity of TAED or DAED.

5.3.1.1.4 Acute Toxicity – Other Routes

There are no studies available.

Conclusion – acute toxicity

TAED and DAED are of very low acute toxicity. The TAED oral LD50 in rats is in the range of 8 g/kg BW, no lethality occurred at TAED and DAED doses of 2 g/kg BW. Based on these data and the results of the dermal absorption study, dermal acute toxicity would be even lower. At the highest TAED exposure concentration tested in an acute inhalation study (264 mg/m^3) no mortality occurred and no clinical signs have been reported.

5.3.1.2 Corrosiveness/Irritation

5.3.1.2.1 Skin Irritation

TAED was tested for primary dermal irritation in three New Zealand White rabbits according to OECD guideline 404 and GLP (Hoechst, 1993a). 30-60 min after the 4 hour semi-occlusive exposure period one animal showed very slight erythema, whereas the treated skin area of the other animals showed no signs of irritation. 24 hours after patch removal until the end of the study no signs of irritation were present in all animals. The study is valid without restrictions (data quality score 1).

In a study using the same experimental layout a TAED formulation consisting of 90% TAED and 10% tallow alkyl ethoxylate was not irritating to rabbit skin (Hoechst, 1986b). This study

was carried out according to OECD guideline 404 and GLP. However, only a short report but not a report according to GLP was written up so that study quality is rated as reliable with restrictions (data quality score 2).

In a study conducted at Safepharm (1982b) according to GLP six New Zealand White rabbits received a single dermal application of 0.5 g TAED on two sites, one abraded and one intact. The test sites were occluded for 24 hours. 1 hour and 48 hours after the removal of the patches and residual test material the test sites of each test animal were observed for evidence of irritation. 1 h after patch removal barely perceptible erythema (Draize score 1) was noticed at 2 of 6 intact sites and 1 of 6 abraded sites, with one of the affected intact sites also showing minimal oedema at this stage (Draize score 1). At the 72 hours reading all evidence of cutaneous irritation had disappeared. Based on these results a primary cutaneous irritation index of 0.17 was calculated and TAED was classified as a mild irritant by the authors. The study is valid without restrictions (data quality score 1).

Groups of 5 male and 5 female hairless mice were treated with a saturated solution of TAED (male mice) once daily or with a 1% suspension in carboxymethyl cellulose twice daily for 10 consecutive days. Immediately after each application the substance was rubbed into the skin. During the treatment period and after the last application no signs of irritation were observed (Henkel, 1980a). The data quality is not assignable, as there is only a brief summary of the study available (data quality score 4).

5.3.1.2.2 Eye Irritation

TAED was tested for eye irritation in three New Zealand albino rabbits according to OECD guideline 405 and GLP (Hoechst, 1993b). One hour after instillation of 0.1 g TAED moistened with 10 µl isotonic saline clear discharge and hyperaemic conjunctivae (Draize score 1) were observed. 24 hours after application until the end of the observation period no sings of irritation were found. The study is valid without restrictions (data quality score 1).
In another study using the same experimental design a TAED formulation consisting of 90% TAED and 10% tallow alkyl ethoxylate was not irritating (Hoechst, 1986c). The study was carried out according to OECD 405 and GLP, but only a short report and not a report according to GLP was written up. It is rated as reliable with restrictions (data quality score 4).
0.1 g TAED was instilled into the conjunctival sac of the right eye of six Zealand White rabbits (Safepharm, 1982c). Minimal palpebral redness was observed in 2/6 rabbits and 1/6 rabbits 24 hours and 48 hours following treatment, respectively. All evidence of irritation had ameliorated at the 72 hour reading.
The study was conducted according to GLP and meets current testing standards. It is reliable without restrictions (data quality score 1).
In a non-GLP study which has to be judged as reliable with restrictions (data quality score 2) 0.1 ml of a 1% TAED formulation in a 2% carboxy methyl cellulose suspension, 0.1 ml of a saturated aqueous TAED solution and 0.1 mg TAED powder were given into the right eyes of four, two and one rabbits, respectively (Henkel, 1980a). After 10 seconds the treated eyes were washed intensively with tab water. Assessment of irritation was made 2, 6, 24, 48 and 72 hours after treatment. No evidence of irritation was apparent in the rabbit treated with the TAED powder. Some rabbits treated with either the 1% TAED formulation or the saturated TAED solution showed slight conjunctival reactions which had disappeared at the 6 hour and 48 hour reading.

Conclusion - Corrosiveness/Irritation

Dermal treatment with **TAED** caused only very slight erythema in some animals and minimal oedema in one animal for a short period of time. Based on these results, TAED is considered as very slightly to non-irritating to the skin.

When tested for eye irritation **TAED** produced only temporarily minor signs of irritation. Based on the effects described above, TAED is considered to be very slightly to non-irritating to eyes.

There are no studies available on **DAED**. However, based on similar physico-chemical properties a skin and eye irritation potential comparable to TAED can be assumed.

5.3.1.3 Sensitization

Two Magnusson-Kligman maximization tests were performed in order to assess the cutaneous sensitizing potential of **TAED** (Safepharm, 1982d and Unilever, 1975). Only the Safepharm study was in accordance with GLP. The experimental details are summarized in table 3. The TAED concentrations used for intradermal injection were quite different in both studies, however, it is reported that the respective concentrations caused definite irritation reactions. Mortality occurred in one animal at day 8 of the Safepharm study. None of the animals died during the Unilever study.

Treated skin areas were examined for erythema and edema upon challenge at 24 and 48 hours after patch removal in the Safepharm study and upon challenge and rechallenge at 4, 24 and 48 hours after patch removal in the Unilever study. None of the test and control animals showed a positive skin reaction. Therefore, TAED is considered to be not sensitizing.

Both studies are judged as reliable with restrictions (data quality score 2), mainly due to the fact that both study reports do not indicate whether a positive control was conducted and the Unilever study was not conducted in accordance with GLP.

Table 3. Experimental details of the Magnusson & Kligman tests performed with TAED.

			'Safepharm Study'		'Unilever Study'	
			Test Group	Control Group	Test Group	Control Group
No. of guinea pigs (sex)			10 (f)	10 (f)	10 (5 m, 5 f)	8 (4 m, 4 f)
Induction	TAED Conc.	Intradermal Application	5% in arachis oil	vehicle only	0.75% in distilled water	vehicle only
		Topical Application	25% in petro-leum jelly BP	vehicle only	20% in distilled water	vehicle only
	SLS Treatment		yes	yes	no	no
TAED Concentration at 1. Challenge			25% in petro-leum jelly BP	25% in petro-leum jelly BP	20% in distilled water	20% in distilled water
TAED Concentration at 2. Challenge			no second challenge	no second challenge	20% in distilled water	20% in distilled water

For human data see section 5.3.1.9.

DAED is reported by Gilbert (1992) as a non-sensitizer in the Magnusson-Kligman test. As there is no reference given, the result cannot be validated (data quality score 4).

Conclusion

Both TAED and DAED are considered to be not sensitizing in guinea pigs. Furthermore, there are no indications of a sensitizing potential in humans (see section 5.3.1.9).

5.3.1.4 Repeated Dose Toxicity

5.3.1.4.1 Oral Administration

Subacute oral toxicity was evaluated in groups of 10 Wistar rats (5 males, 5 females) receiving TAED by once daily gavage at dose levels of 0, 40, 200 and 1000 mg/kg BW and day for 28 days (RCC, 1989).

Mortality, clinical abnormalities, ophthalmoscopic findings and toxicologically relevant changes of hematological, biochemical and urinalysis parameters were not observed throughout the study. Food consumption in male rats of the high dose group and female rats of the high and mid dose group was significantly less than the controls during treatment days 1 to 8. The same occurred in female rats of the high dose group during treatment days 15 to 28. The body weights and body weight gains of the high dose female rats were significantly lower than control from day 15 until the end of the 28 day treatment period. A significant increase of absolute and relative liver weights was found in male and female rats of the 1000 mg/kg BW group. Male rats of this group showed also significantly reduced absolute and relative spleen weights. Histopathological examination revealed slight hepatic centrilobular parenchymal hypertrophy, consistent with enzyme induction, in male and female rats of the

high dose group. The lower dose levels produced no pathological evidence of toxicity. Based upon the results a “no-adverse-effect-level” of 200 mg/kg BW/day was determined. The study was performed according to OECD guideline 407 and GLP and is therefore reliable without restrictions (data quality score 1).
TAED was given orally for 90 consecutive days to groups of 10 Sprague-Dawley rats per sex at dose levels of 0, 25, 500, and 1000 mg/kg BW/d (TherImmune Research Corporation, 2000a).
All animals survived to the scheduled termination and no treatment-related clinical signs were noted. Decreased body weights were found in all male groups and the mid- and high-dose females. Food consumption was decreased in the high-dose males. Increased absolute and relative liver weights and liver hypertrophy were observed at the mid- and high-dose males and females. In the clinical pathology there were significant increases in the red blood cells, total protein, albumin and cholesterol, and decreases in hemoglobin, hematrocrit, MCV, MCH, glucose, creatine, AST, chloride and triglycerides.
Based on body weight changes there would be no “no-observed-effect-level” (NOEL) in the males and a NOEL of 25 mg/kg BW/d in females. Based on microscopic changes the NOAEL and NOEL would be 25 mg/kg BW/d in males and females.
There is only a summary of the study available containing the information given above. The significance of the indicated changes in clinical pathology parameters remains unclear as they were just listed and not discussed in relation to dosing, sex, and present or historical control. Based on the available data it looks like decreased body weights occurred in all male groups including the control and that there was no dose relationship. However, it remains unclear if this was truly the case. Also, the very large interval of a factor of 25 between the mid- and low-dose limits the value of the determined NOEL. Based on the summary data quality is rated as not reliable (data quality score 3).

Subchronic oral toxicity was evaluated in groups of 10 male and 10 female Sprague-Dawley rats receiving TAED by gavage at daily dose levels of 0, 90, 250 and 800 mg/kg BW for 90 days (Henkel, 1987). A recovery control and high dose group consisting of 5 male and 5 female rats was terminated 28 days after the 90 day treatment period.
Mortality did not occur. Salivation observed in the animals of the high dose group was the only clinical finding. Water consumption was increased in males of the 250 and 800 mg/kg BW/d group and in all female test groups, whereas food consumption was not affected. Total body weight gain was decreased in male and female rats of all high dose groups. Slightly

decreased haematocrit values in all male test groups and an increase in leukocytes in females of the high dose were observed. Changes in biochemical parameters considered to be compound-related comprised increased protein values in male and female rats of the high dose group and increased cholesterol values in female animals treated with 800 mg/kg BW. Eye examination revealed no compound related findings. At the dose level of 250 mg/kg BW relative liver and testes weights were significantly increased in male rats. At 800 mg/kg BW absolute and relative liver weights of both sexes and relative adrenal and testes weights in male rats were statistically significantly increased. No compound related macroscopically visible findings were present at necropsy. Histopathological examination revealed centrilobular hypertrophy of hepatocytes in all high dose animals. This effect reversed completely within the 28 day recovery period. In the animals of the low and mid dose group centrilobular hypertrophy was borderline in some rats and not considered a clear substance related effect, since this finding was also present in some control animals of the recovery group.

Clear substance related adverse effects occurred at the dose level of 800 mg/kg BW/d. Changes in organ weights were present at 250 mg/kg BW/d. No adverse effects were observed at 90 mg/kg BW/day. Hence, a “no-adverse-effect-level” of 90 mg/kg BW/day can be deduced.

The study was performed according to OECD guideline 408 and GLP and is therefore reliable without restrictions (data quality score 1).

Conclusion

TAED has a low toxicity when administered repeatedly by oral gavage. Centrilobular hypertrophy of hepatocytes is the only toxicologically significant finding. It occurs only at high concentrations, is reversible and thus, rather a phenomenon of adaptation than a real adverse effect. The most conservative “no-adverse-effect-level” which can de deduced from the studies is 90 mg/kg BW/day.

For **DAED** Gilbert (1992) indicates a NOEL of 5700 mg/kg BW/d in a 13-week rat feeding study. As there is no reference given, the result cannot be validated (data quality score 4).

5.3.1.4.2 Inhalation

Subacute inhalation toxicity was evaluated in 10 male and 10 female Wistar rats exposed in inhalation chambers to **TAED** dust for 23 consecutive working days, 5 hours/day, at levels of 141 mg/m^3 on day 1, 145 mg/m^3 on day 2-10, 212 mg/ m^3 on day 11-15 and 508 mg/ m^3 on day 16-23 (Henkel, 1980a,b). A mean TAED concentration of 283 mg/m^3 was calculated for the total treatment period. A control group of 10 male and 10 female animals was included in the study.

All animals survived the exposure period. The body weights and body weight gains of the treated animals did not differ from the control rats. According to the study report, clinical signs were not recorded during the treatment period. No macroscopically visible changes were observed at necropsy. Liver and kidney weights, which were the only organ weights determined, were comparable to control. Histopathological examination of the respiratory system, liver and kidneys revealed no substance-related effects.

The study cannot be subsumed under a testing guideline and was not performed in accordance with GLP, however, is well documented and scientifically acceptable. The investigation is rated as reliable with restrictions (data quality score 2).

In a subchronic inhalation study three groups of 12 Wistar male rats were exposed in inhalation chambers to mean concentrations of TAED dust (< 3.5 µm) of 12.2, 60.3 and 99.7 mg/m3 for 6 hours a day, 5 days a week, for 13 weeks (Unilever, 1981). A control group of 12 male rats was sham-exposed. Male rats were used, as they were more sensitive than females in the acute inhalation study. Following exposure, 6 rats from each group were killed and examined by whole body necropsy. The remaining rats were maintained without further treatment for 13 weeks to investigate the reversibility of any treatment-related effects. Mortality did not occur. There were statistically significant increases in absolute and relative liver and kidney weights. All organ weights returned to normal values following the recovery period, apart from a small increase in liver weight at the high dose. There was a statistically significant reduction in hemoglobin and an increase in platelet numbers in the rats exposed to the high level of TAED, and an increase in the number of monocytes in the high and mid level exposure groups. These values were within normal limits following the 13-week recovery period. Levels of glucose and aspartate transaminase activity were reduced in all TAED exposure groups. Increased Ca2+ , serum total protein and albumin and reduced alanine transaminase activity were found in the high and mid-exposure groups, and increases in total

cholesterol and pseudocholinesterase activity and reduced alkaline phosphatase activity in the high level group. The values had returned to normal after the recovery period. At post-mortem, one rat exposed to the high level of TAED had a slight enlargement of the liver, otherwise no abnormal features were observed in any of the rats. Microscopic examination showed no treatment-induced effects in the lungs. There was a systemic response as evidenced by significant increases in kidney weights in the high and mid exposure groups, and in liver weights in all exposure groups. This was reflected in changes in hepatic and renal morphology. The morphological change seen in the liver was hypertrophy of centrilobular hepatocytes. This was considered to be due to induction of hepatic microsomal drug metabolizing enzymes, based on further ultrastructural studies that demonstrated proliferation of smooth endoplasmatic reticulum in these hepatocytes. The morphological changes found in the kidneys were eosinophilic droplets in the tubular epithelial cells, usually referred to as hyaline droplets composed principally of the normal male rat urinary protein α2µ-globulin. The fact that in another Unilever study female rats fed TAED did not develop this pathology, but males did, confirms this to be the case (Carthew, 2001). The kidney findings are therefore specific to the male rat and not relevant to humans. Examination of recovery rats showed that these effects reversed completely during a 13-week recovery period.

The NOAEL for systemic effects cannot be derived from this study as the whole body of the animals was exposed to TAED dust and the oral ingestion of unquantifiable amounts of substance would have occurred due to grooming.

Under the conditions of this study, repeated exposure by inhalation to TAED dust at doses up to 99.7 mg/m3 did not cause any adverse effects in the rat lung, respiratory tract or nasal mucosa.

The study was done to GLP and while the report does not state whether it was conducted to a recognized guideline it met the requirements of OECD Test Guideline No. 413. However, small group sizes were used. The study is therefore valid with restrictions (data quality score 2, assigned by Unilever (Moran, 2002)).

There is no study available on **DAED**.

5.3.1.4.3 Dermal Administration

Subchronic dermal toxicity was studied in groups of 10 female and 10 male Sprague-Dawley rats for 90 days according to OPPTS Guideline No. 870.3250 (TherImmune Research Corporation, 2000b). **TAED** pasted in 1% carboxymethylcellulose (CMC) was applied dermally once daily for 6 hours at 0, 20, 200, and 2000 mg/kg BW/d. A gauze pad with the test article formulation was placed on the dorsal surface covering the shaved area of approximately 10% of the body surface and secured with vet wrap held in position by taping the ends. At the end of the exposure, the animals were unwrapped and the exposure area was wiped with gauze moistened with 1% CMC. Following the treatment period, all animals were weighed then euthanised by carbon dioxide asphyxation and ensanguined and subsequently necropsied.

One control male, two 200 mg/kg BW/d females, and one 2000 mg/kg BW/d female did not survive to termination. These deaths were considered to be the result of the wrapping procedure and not the effect of TAED since no clinical signs suggestive of TAED involvement were noted prior to death. No treatment related findings were noted at 0, 20, or 200 mg/kg BW/d in clinical observation, body weight and food consumption data, ophthalmologic findings, clinical pathology findings, gross necropsy, and organ weights. The only treatment-related finding was at the high dose, 2000 mg/kg BW/d, which was hypertrophy of centrilobular hepatocytes in 8/10 and 4/10 females and males, respectively, and graded minimal in degree of severity. The centrilobular hypertrophy seen in these livers was similar to that observed in the livers of rats administered TAED via oral gavage in a 90 day study (Therimmune Research Corporation, 2000a), except the degree of change in this dermal study was much less and not all high-dose animals were affected.

Based on the effects in this study the NOEL would be equal or greater than 200 mg/kg BW/d in both males and females. The NOEL of 200 mg/kg BW/d is a result of the large factor of 10 between dose levels. Based on the minimal effects observed in this study an actual NOEL much closer to 2000 mg/kg BW/d can be assumed.

The study is reliable without restriction (data quality score 1).

There is no study available on **DAED**.

Conclusion – repeated dose toxicity

Repeated dose oral studies revealed that TAED reduces body weigh gain and causes reversible centrilobular hypertrophy in the liver at high doses due to the induction of metabolizing enzymes. This effect was also found in a subchronic whole body inhalation study. No adverse effects in the rat lung, respiratory tract or nasal mucosa were observed. Upon repeated dermal administration the same systemic effect of centrilobular hypertrophy was observed, however only at the highest dose tested (2000 mg/kg BW/d) and minimal in degree of severity.

For DAED a NOEL of 5700 mg/kg BW/d has been reported in a 90-day rat feeding study, which indicates that DAED is even less toxic than TAED. Thus, it can be assumed that repeated dermal application and inhalation are also of no concern.

5.3.1.5 Genetic Toxicity

5.3.1.5.1 In Vitro

a) Bacterial Mutation Tests

TAED was assessed for its potential to induce gene mutations in two bacterial reverse mutation assays.

In the assay performed at Safepharm Laboratories (1982e) TAED was tested at concentrations of 10, 100, 1000 and 10000 µg/plate with and without S9-mix (microsomal fraction from phenobarbitol/5,6-benzoflavone induced rat livers) using Salmonella typhimurium strains TA 100, TA 1535, TA 98, TA 1537 and TA 1538. Each concentration, including solvent and positive controls, was tested in triplicate. DMSO was used as solvent/diluent for TAED. No indication is given whether TAED was soluble or remained undissolved at the various concentrations. The test substance did neither cause toxic effects nor an increase in revertant colony numbers in the Salmonella typhimurium strains used.

In conclusion, TAED was not mutagenic under the experimental conditions described.

The study does not comply with the current testing guideline, but is overall well documented and scientifically acceptable and therefore rated as reliable with restrictions (data quality score 2).

In a second study (CCR, 1988) TAED was tested in the plate incorporation assay at concentrations of 10, 33.3, 100, 333.3 and 500 µg/plate using the Salmonella typhimurium strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 and in addition the Escherichia coli strain WP2 with and without S9-mix (microsomal fraction from Aroclor 1254 induced rat livers). Two independent experiments were performed. Each concentration, including negative, solvent and positive controls, was tested in triplicate. Deionized H_2O was chosen as solvent for TAED. 500 µg/plate was selected as the highest test concentration, since the test substance was partially insoluble at this concentration. Alternative solvents like DMSO, DMF, ethanol or acetone showed no better solubility properties. No distinct toxic effects occurred in the test groups. Up to the highest dose, no significant and reproducible increase in revertant colony numbers was obtained in any of the strains used.

TAED did not induce mutations in the genome of the bacterial strains used.

The study is in accordance with common test guidelines and GLP and therefore rated as reliable without restrictions (data quality score 1).

The potential of **DAED** to induce histidine (his) reversion (his- to his+) and tryptophane (tryp) reversion (tryp- to tryp+) in the genomes of S. typhimurium and E. coli was evaluated in the Reverse Mutation Assay (Ames Assay) according to GLP (Toxikon Corporation, 2000b). This direct plate incorporation assay was conducted with four strains of S. typhimurium (TA 98, TA 100, TA 1535, TA 1537) and one of E coli (WP2) in the presence and absence of an exogenous mammalian activation system (S9 mix using Aroclor 1254 induced rat livers). Prior to the main study a range finding assay was performed using TA 100 without metabolic activation to determine the cytotoxicity of the test substance. DAED assayed at concentrations from 0.1 µg/plate to 10000 µg/plate in triplicates was not cytotoxic and not mutagenic. In the main study, DAED was tested at 5000 µg/plate. Isotonic saline was chosen as solvent. DAED, solvent, and positive controls, were tested in triplicate. A confirmatory assay was performed in order to verify the result of the Reverse Mutation Assay. A statistically significant increase in the number of colonies was not observed with the test article. Based on the criteria of the study protocol, DAED is considered non-mutagenic.
The study does not fully comply with the OECD test guideline No. 471, but is well documented and scientifically acceptable and therefore rated as reliable with restrictions (data quality score 2).

b) Chromosome Aberration test

The potential of **TAED** to induce structural chromosome aberrations was assessed in V79 cells of the Chinese hamster (CCR, 1989) and in human lymphocytes in vitro (Safepharm Laboratories, 1995a). Both studies were conducted according to the OECD testing guideline 473 in force at the time of test performance and GLP. They are reliable without restrictions (data quality score 1).
Duplicate human lymphocyte cultures were treated with the test substance and evaluated for chromosome aberrations, together with vehicle (PEG 400) and positive controls. Four treatment conditions were used: 4 hours of exposure in the presence of S9-mix with cell harvest 20 hours and 44 hours after start of treatment, and a 20 and 44 hour continuous exposure in the absence of activation. Two independent experiments were performed. In experiment 1 (20 hour harvest) cultures were exposed to 8 concentrations of TAED. The solubility properties of TAED at the given concentrations in the culture medium is not reported. The three highest concentrations (570, 1140 and 2280 µg/ml (equivalent to 10 mM)) were selected for chromosomal analysis. In experiment 2, cultures were exposed to TAED at 570, 1140 and 2280 µg/ml (20 hour harvest), or 2280 µg/ml (44 hour harvest). There was no

real evidence of toxicity of TAED at the 20 hour harvest, but at the 44 hour harvest mean mitotic indices were reduced to approximately 65% of the vehicle control value, both in the presence and absence of S9-mix.
Chromosomal analysis revealed that TAED induced no biologically or reproducible, statistically significant increases in the frequency of cells with aberrations.
TAED was shown to be non-clastogenic to human lymphocytes in vitro.
Duplicate cultures of V79 cells were treated with TAED for 4 hours in the presence and absence of S9-mix, harvested at 7 hours, 18 hours and 28 hours after start of treatment and evaluated for chromosome aberrations. Solvent and positive controls were included in the study. TAED concentrations tested were 500 µg/ml in cultures harvested after 7 or 28 hours and 20, 200 and 500 µg/ml in cultures harvested after 18 hours. 500 µg/ml was chosen as the maximum concentration, because higher concentrations could not be dissolved in the culture medium. The mitotic index was only slightly reduced at 500 µg/ml at the 7 h harvest in the presence and absence of S9-mix. There was no relevant increase in cells with structural aberrations.
TAED was non-clastogenic to V79 cells of the Chinese hamster in vitro under the experimental conditions used.
There is no test available on **DAED**.

5.3.1.5.2 In Vivo

TAED was tested for the incidence of chromosomal alterations in the micronucleus test in groups of 14 albino CF1/W68 mice (7 males and 7 females) at dose levels of 250, 1250 and 2500 mg/kg BW given twice, separated by an interval of 24 hours, by oral gavage (Henkel KgaA, 1984). Negative and positive control groups receiving the vehicle, carboxymethyl cellulose (1%)/cremophor (0.5%), or cyclophosphamide were also included. The animals were sacrificed 30 hours after the first substance application and bone marrow smears from both femurs were prepared. No premature deaths occurred. At all dose levels the group mean micronucleated cell count of TAED was comparable with the concurrent negative control value. No significant change in the ratio of polychromatic/normochromatic erythrocytes was observed, but the presence of clinical observations indicated that systemic absorption had occurred.
In conclusion, TAED was considered to be non-mutagenic under the conditions of the test.
This well documented study was not performed in accordance with GLP and is therefore rated as reliable with restrictions (data quality score 2).

In a further micronucleus test (Safepharm Laboratories, 1995b), groups of 10 albino CD-1 mice (5 males and 5 females) were given a single oral dose of TAED at 312.5, 625 and 1250 mg/kg BW. Negative and positive control groups receiving the vehicle, arachis oil, or cyclophosphamide were also included. Control and high dose animals were killed 24, 48 and 72 hours after dosing; animals of intermediate and low dosage groups as well as the positive control group were killed 24 hours after dosing. Bone marrow was extracted from the femurs and smear preparations were made and stained. Three premature deaths were observed after dosing with 1250 mg/kg BW. There were no statistically significant increases in the frequency of micronucleated polychromatic erythrocytes in animals dosed with TAED when compared to the concurrent vehicle control groups. No significant change in the ratio of polychromatic/normochromatic erythrocytes was observed, but the presence of clinical observations and premature deaths at the high dose level indicated that systemic absorption had occurred.
In conclusion, TAED was considered to be non-genotoxic under the conditions of the test. The test was performed according to OECD test guideline 474 and GLP and is reliable without restrictions (data quality score 1).
There is no study available on **DAED**.

Conclusion – genetic toxicity
TAED was non-mutagenic in bacterial reverse mutation assays, non-castogenic in V79 calls and human lymphocyte cultures and non-mutagenic in the micronucleus test in vivo.
DAED was non-mutagenic in the bacterial reverse mutation assay. Further tests are not available. However, based on the structure, physico-chemical properties similar to TAED and the fact, that DAED is the main in vivo metabolite of TAED, data on TAED can be used as bridging data.

5.3.1.6 Carcinogenicity

There are no studies available. However, given the negative test results on genotoxicity (section 5.3.1.5), the outcome of the repeated dose studies showing no indication of pre-neoplastic changes (section 5.3.1.4) and the biokinetic data demonstrating complete and fast excretion of the formed metabolites (section 5.3.1.9.1), there is no concern regarding carcinogenicity.

5.3.1.7 Toxicity to Reproduction

There are no studies available. However, as no effects on the reproductive organs have been found in the 90-day repeated dose studies, it can be assumed that this endpoint is of no concern.

5.3.1.8 Developmental Toxicity/Teratogenicity

Teratogenicity was evaluated in groups of 25 pregnant Sprague-Dawley rats treated with **TAED** by gavage at dose levels of 0, 40, 200 and 1000 mg/kg BW/day from day 6 to 15 of pregnancy (RBM, 1994). The dams were caesarean-sectioned on day 20 of gestation and subjected to post-mortem examination. No clinical signs, behavioral changes, death or abortion were noted in any group. A dose-related lower mean body weight gain and mean daily food consumption was observed at 200 and 1000 mg/kg BW/day.
No embryotoxic effects were found. Visceral and skeletal malformations or anomalies were not significantly increased at all dose levels in comparison to the controls. Mean fetal and mean placental weight were significantly decreased and the percentage of skeletal variants was significantly increased at the high dose.
The “no observed effect level” for rat dams was 40 mg/kg BW/day and for fetuses 200 mg/kg BW/day.
The study was performed according to OECD guideline 414 and GLP and is therefore reliable without restrictions (data quality score 1).

Conclusion
TAED was not embryo- or fetotoxic. The observed effects (reduced fetal weight and increased skeletal variants) were only present at the maternally toxic dose level of 2000 mg/kg BW/day.
There is no study available on **DAED**. As DAED is a main metabolite of TAED and thus has been examined in the TAED teratogenicity study as well, it can be concluded that DAED is of no concern regarding this endpoint.

5.3.1.9 Additional Data

5.3.1.9.1 Biokinetics

The fates of tetra acetyl [^{14}C]ethylene diamine (TA[^{14}C]ED) and [1-^{14}C]tetra acetyl ethylene diamine ([^{14}C]TAED) were followed in groups of 3 male and 3 female Wistar rats after oral intubation with 0.5 ml dietary slurry containing 5 mg TA[^{14}C]ED or 4.6 mg [^{14}C]TAED (Unilever, 1978a). The nature of the radio-labelled compounds in urine and feces was studied and ^{14}C levels were monitored in tissues, carcass remains, urine and feces. A further group of rats was intubated with [^{14}C]TAED and killed at 1, 2, 4, 7 and 24 hours to monitor the rate of absorption from the intestine and uptake by the liver, adrenal and kidney tissues.
Monitored ^{14}C levels are depicted in table 4. There was no sex difference in the absorption, metabolism and excretion of TA[^{14}C]ED and [^{14}C]TAED.
At one hour after dosing more than 50% of the administered ^{14}C had been absorbed from the intestine. Tissue levels of ^{14}C were at their highest at 2 hours after dosing. Subsequently levels fell rapidly except in the adrenal gland where ^{14}C levels rose during the 7 hours after dosing. More than 90% of the urinary ^{14}C was excreted within 24 hours of dosing.
Chromatographic analysis showed only traces of TAED in the urine. Most of the ^{14}C was excreted as triacetyl ethylene diamine (TriAED) and diacetyl ethylene diamine (DAED). Mono acetyl ethylene diamine (MAED) and ethylene diamine were not found.
The results show that TAED was rapidly absorbed from the rat intestine and was largely metabolized and excreted in the urine within 24 hours. Differences in the levels of ^{14}C recovered as expired CO_2 reflect the different metabolic fates of the acetyl and ethylene diamine moieties. The ^{14}C compounds identified in the urine, TirAED and DAED, indicate that deacetylation was the main metabolic route for TAED in the rat.

Table 4. ^{14}C recoveries from rats after oral intubation with TA[^{14}C]ED or [^{14}C]TAED.

	Mean % recoveries of ^{14}C from rats	
	2 days after [^{14}C]TAED admin.	4 days after TA[^{14}C]ED admin.
Urine	67.3	97.7
Feces	2.8	3.4
Expired air	17.9	0.4
Carcass	3.1	1.0
Total	91.1	102.5

The study was conducted prior to GLP and while it was not done according to any recognized guideline it meets many of the requirements of OECD Test Guideline No. 417. It is also well

documented, conducted and scientifically acceptable and therefore ranked as valid with restrictions (data quality score 2, assigned by Unilever (Moran, 2002)).

According to Gilbert (2002) radioactive traced **DAED** is rapidly absorbed from the gastrointestinal tract of rats following oral intubation and rapidly excreted unchanged via the urine. As there is only the result given in the publication but no reference, data quality cannot be assigned (score 4).

5.3.1.9.2 Skin Penetration

Skin penetration studies using TA[^{14}C]ED in detergent solutions and in chloroform were conducted in rats (Unilever, 1978b). One group of Wistar rats was treated with 0.2 ml of a 1% w/v detergent A base containing 400 µg TA[^{14}C]ED applied over 10 cm^2 of clipped dorsal skin. A second group was treated with 200 µl of a solution containing 6% powder detergent B base, 1% perborate and 0.5% TA[^{14}C]ED (1348 µg TA[^{14}C]ED) and a third group was treated with 50 µl chloroform containing 1124±40µg TA[^{14}C]ED. The amounts of TA[^{14}C]ED penetrating skin are given in table 5.

Of the TA[^{14}C]ED which penetrated the skin, most was recovered in the urine while less than 3% was recovered in the feces.

The results indicate, that TAED can principally penetrate rat skin, increased contact time leading to increased penetration.

The study was conducted prior to GLP and while it was not done according to any recognized guideline it meets many of the requirements of OECD Test Guideline No. 417. It is also well documented, conducted and scientifically acceptable and therefore ranked as valid with restrictions (data quality score 2, assigned by Unilever (Moran, 2002)).

Table 5. Skin penetration of TA[^{14}C]ED in rats.

Vehicle	Duration of contact before rinsing (min)	Amount of TA[^{14}C]ED in µg/cm^2 applied to skin	penetrating skin after 2 days	% of applied TA[^{14}C]ED penetrating skin
Detergent A	1	40	0.05	0.13
base	5	40	0.18	0.45
	10	40	0.39	0.98
	20	40	0.69	1.73
Detergent B	1	134.8	0.2	0.15
base + perborate	10	134.8	1.2	0.89
Chloroform	left on skin	112.4	4.8	4.27

There is no study available on **DAED**.

5.3.1.10 Experience with Human Exposure

Approximately 200 workers in the Wiesbaden production plant and laboratory of Clariant have been monitored over the last 21 years. The employees have been examined in frequencies of one to two years since 1981. The examination included blood, lung function and ECG. At no time evidence of systemic, generalized or local reactions due to TAED have been found, especially no allergic reactions or skin irritations occurred (Cramer, 2001). According to IVDK (Information Network of Departments of Dermatology in Germany), where cases of skin sensitization are collected and evaluated centrally in Germany, cases of TAED-allergy have not been observed over the past 10 years, despite its widespread use (Schnuch, 2002).

5.3.2 Identification of Critical Endpoints

5.3.2.1 Overview on Hazard Identification

The acute toxicity of **TAED** is very low. The rat oral LD50 is in the range of 8 g/kg. No lethality occurred at 2 g/kg. Clinical signs present at this dose comprised subdued activity, labored respiration, hunched appearance and ataxia. The oral LD50 in mice is 5.9 g/kg. There is no acute dermal toxicity study available. However, the results of the dermal absorption study indicate, that only a low percentage of TAED is able to penetrate skin. It can be therefore assumed that dermal acute toxicity is even lower than oral acute toxicity. At the

highest exposure concentration tested in an acute inhalation study (264 mg/m^3) no mortality occurred and no clinical signs have been reported.
TAED is practically non-irritating to skin and eyes and there is no evidence of a sensitizing potential by skin contact both in guinea pigs and in humans.
Subacute and subchronic oral studies revealed that TAED reduces body weight gain and causes the reversible adverse effect in the liver of centrilobular parenchymal hypertrophy at high doses. This effect was consistent with the increase of liver weight and can be attributed to the induction of metabolizing enzymes. The reported changes in some hematology and clinical chemistry parameters are considered to be of no toxicological relevance, since they were isolated findings, not corroborated by clinical observations or anatomical pathology findings. Changes in spleen, adrenal and testes weights were reported as well. However, they occurred only in single studies and were not accompanied by any histopathological findings. They are therefore considered as incidental findings without toxicological relevance.
The effect of centrilobular parenchymal hypertrophy was also found in a subchronic whole body inhalation study. No adverse effects in the rat lung, respiratory tract or nasal mucosa were observed.
Upon dermal administration the same systemic effects can be expected as observed after oral application, since small amounts of TAED can penetrate rat skin. This has been confirmed in a 90-day repeated dose dermal study in rats, where the only treatment-related finding was at the high dose, 2000 mg/kg BW/d, which was minimal centrilobular hypertrophy in 8/10 and 4/10 females and males, respectively.
Various bacterial mutation, in vitro chromosomal aberration and in vivo micronucleus tests did not indicate a genotoxic potential of TAED.
TAED was not teratogenic. A decrease in mean fetal weight and an increase of the percentage of skeletal variants occurred only at the maternally toxic dose of 1000 mg/kg BW/d.
Biokinetic data showed that TAED is rapidly absorbed from the rat intestine and largely metabolized via diacetylation to TriAED and DAED which are excreted in the urine to more than 90% within 24 hours.
Skin penetration studies indicated, that pure TAED or TAED present in solutions of detergent bases can penetrate rat skin. 0.13% of the applied TAED amount penetrated the skin when contact time was 1 min and 4.3% when contact time was raised to 2 days.
Chronic toxicity, carcinogenicity, fertility and late stages of developmental toxicity (from birth to sexual maturity of offspring) have not been addressed so far. Based on the chemical

structure, the available toxicity and kinetic data it can be expected that TAED would cause no concern with respect to carcinogenicity, fertility and the late stages of developmental toxicity.

There are only a few toxicity data available on **DAED** and they all indicate very low toxicity: There was no acute oral toxicity at 2000 mg DAED/kg BW, DAED was not mutagenic in the Ames test, and Gilbert (1992) reported DAED as a non-sensitizer in the Magnusson & Kligman test, as rapidly absorbed and excreted via urine and as basically non-toxic in a 13 week rat feeding study (NOEL = 5700 mg/kg BW/d).
For all other endpoints, data on TAED can be used as bridging data because the physical-chemical properties of both substances are very similar, and TAED completely hydrolyzes to DAED in aqueous media within a few hours (Hirschen and Meuth, 2002) and largely metabolizes to DAED in vivo, so that whenever TAED is studied DAED is evaluated as well.

5.3.2.2 Critical Endpoints

The most relevant endpoints with regard to possible consumer exposure are long term dermal and oral uptake of TAED and DAED.

The eye irritation potential and the acute oral toxicity of both substances are also important endpoints, since they are needed to assess accidental exposure and intentional over exposure. Furthermore, skin sensitization and skin irritation will be assessed, although TAED as well as DAED are of no concern regarding these endpoints.

5.3.3 Determination of NOAEL or Quantitative Evaluation of Data

The only toxicologically relevant effect following repeated oral and dermal administration as well as repeated whole body inhalation of TAED was hepatic centrilobular hypertrophy. Its reversibility was demonstrated in the 90-day oral gavage study. The NOAELs for this effect that have been deduced from the 28-day and 90-day oral rat toxicity study are 200 and 250 mg/kg BW/d, respectively. As relative liver weights were still significantly increased in male rats at the dose level of 250 mg/kg BW in the 90-day study, the conservative NOAEL of 90 mg/kg BW/d was finally deduced, which also represents the systemic NOAEL as the absorption of TAED is close to 100%.

Based on this NOAEL and the results from the skin penetration study (4.3% penetration) a NO(A)EL in the range of 2000 mg/kg BW would be expected upon repeated dermal administration. From the 90-day dermal study a NOEL equal to or greater than 200 mg/kg BW/d was deduced. However, taking into account the large interval of factor 10 between dosages used in this study and that minimal centrilobular hypertrophy was the only effect in the 2000 mg/kg BW/d group affecting only 60% of the animals whereas 40% had no effects, it can be assumed that the actual NO(A)EL is not 200 mg/kg BW but close to 2000 mg/kg BW.

Thus, the **NOAEL of 90 mg/kg BW/d** as deduced from the 90-day gavage study is based on the more reliable study and will be used for risk assessment.

The TAED teratology study determined a NOEL of 200 mg/kg BW/d for rat fetuses and 40 mg/kg BW/d for the dams. The NOEL for dams is based on a dose-related lower mean body weight gain and a lower mean daily food consumption. Both findings were not associated with clinical abnormalities or with the induction of any effects related to pregnancy. Only minor effects were observed on fetuses (decreases mean fetal weight and higher percentage of skeletal variants) and occurred solely at the highest dose of 1000 mg/kg BW/d which caused overt maternal toxicity. The NOAEL of 90 mg/kg BW/d from the 90-day oral study is therefore considered to be more relevant with respect to human risk assessment.

Gilbert (1992) reports a NOEL of 5700 mg DAED/kg BW/d in a 90-day feeding study. Unfortunately, that is the only information given by Gilbert and it has not been possible to trace the original study. Thus, the result remains unconfirmed. However, based on the fact that upon absorption in the gastrointestinal tract DAED is rapidly excreted unchanged via urine, and that the only significant effect induced by TAED is due to metabolism in the liver,

a higher NOEL of DAED can be expected in comparison to TAED. The **NOEL of 5700 mg/kg BW/d** is therefore plausible and taken to assess systemic **DAED** exposure.

For accidental exposure or intentional ingestion a dose of 2000 mg/kg BW is used for both TAED and DAED, as no lethality occurred at this dose (LD0).

5.4 Risk Assessment

5.4.1 Margin of Exposure Calculation

The contact scenarios relevant for TAED and DAED have been identified in section 5.2.1.

Skin sensitization

Skin sensitization is of no concern, as TAED did not cause any skin reactions in two guinea pig maximization studies and also DAED is reported negative in a maximization study. Furthermore, no cases of TAED-allergy have been observed in Germany over the last past 10 years, despite its widespread use (Schnuch, 2002).

Local effects on skin or eyes

Local effects on skin are also of no concern since contact time is low (< 1 min when touching powder or tablet, ≤ 10 min during handwashing) and the irritating potential is very low – if any.

Accidental contact of TAED in powder products or TAED/DAED in wash solutions with the eyes is not expected to cause irritation on the basis of the experimental data.

Accidental ingestion or intentional over exposure

Accidental ingestion or intentional over exposure are assumed as rare events. A single swallow of about 5 g will probably be all that can be ingested. This corresponds to 0.44 g TAED, based on the highest TAED content of 8.7% present in powder bleach. Based on the kinetic data which indicate a bioavailability of 100% the resulting systemic dose is 7.25 mg/kg BW for adults and 44 mg/kg BW for young children assuming a body weight of 60 and 10 kg, respectively. This dose is still far below the highest non-lethal dose of 2000 mg/kg BW observed in acute oral studies in rats.

Accidental ingestion of DAED can only occur when drinking some wash solution. However, the concentration of DAED in the wash solution as well as the amount ingested will be so small that no concern arises.

Systemic exposure

Based on the systemic consumer exposures estimated in section 5.2.3 and the NOAELs of 90 mg/kg BW/d and 5700 mg/kg BW/d for TAED and DAED, respectively, the following margin of exposures (MOE) have been calculated:

Table 6. Margin of exposure calculation.

Contact scenario	TAED		DAED	
	Exp_{sys} (mg/kg BW/d)	**MOE**[1]	Exp_{sys} (mg/kg BW/d)	**MOE**[1]
Dermal exposure				
Contact with clothes containing product	0.51×10^{-6}	**180×10^6**	31.7×10^{-6}	**180×10^6**
Direct skin contact via handwashing	11.5×10^{-6}	**7.8×10^6**	7.2×10^{-6}	**790×10^6**
Oral Ingestion				
Residues on dishes and eating utensils	0.75×10^{-6}	**120×10^6**	50×10^{-6}	**114×10^6**
Inhalation	0.029×10^{-6}	**3200×10^6**	none	-
Total	*12.8×10^{-6}*	***7.03×10^6***	*88.9×10^{-6}*	***64.1×10^6***

[1] MOE = NO(A)EL in mg/kg BW/d (90 and 5700 for TAED and DAED, respectively) divided by systemic exposure in mg/kg BW/d

5.4.2 Risk Characterisation

Assessment of the contact scenarios revealed only marginal consumer exposure to TAED and the perhydrolysis product DAED via intended use of TAED containing products. As a result, the MOEs for the total TAED and DAED estimated systemic dose are extremely high (7,030,000 and 64,100,000, respectively), and thus, there is no concern to human health. Also accidental exposure or intentional overexposure is of no concern due to the very low acute toxicity of both substances.

It can be concluded that TAED contained in consumer washing and dish washing products as well as the amount of DAED formed during the wash-process do not cause any risk to human health.

5.4.3 Summary and Conclusion

TAED is used as bleaching activator in various consumers products. Product types within the scope of HERA's targeted risk assessment approach include heavy duty washing and machine dishwashing powders and tablets and bleach boosters. Typical concentrations range between 1.4% and 13% in these products. During the wash-process >99% of TAED is converted to DAED.

TAED is of very low acute and repeat dose toxicity by all exposure routes examined.

The oral LD50 in rats is in the range of 8 g/kg, no lethality occurred at 2 g/kg. Based on these data and the results of the dermal absorption study, dermal acute toxicity would be even lower. At the highest exposure concentration tested in an acute inhalation study (264 mg/m^3) no mortality occurred and no clinical signs have been reported.

TAED is practically non-irritating to skin and eyes and there is no evidence of a sensitizing potential by skin contact both in guinea pigs and in humans.

Subacute and subchronic oral studies revealed that TAED reduces body weight gain and causes reversible centrilobular hypertrophy in the liver at high doses due to the induction of metabolizing enzymes. This effect was also found in a subchronic whole body inhalation study. No adverse effects in the rat lung, respiratory tract or nasal mucosa were observed.

Upon dermal administration the same systemic effects would be expected as observed after oral application, since small amounts of TAED can penetrate rat skin. This has been confirmed in a 90-day repeated dose dermal study in rats, where the only treatment-related finding was at the high dose, 2000 mg/kg BW/d, which was minimal centrilobular hypertrophy.

Various bacterial mutation, in vitro chromosomal aberration and in vivo micronucleus tests did not indicate a genotoxic potential of TAED.

TAED was not teratogenic, but decreased mean fetal weight and increased the percentage of skeletal variants at the highest test dose of 1000 mg/kg BW/d, which, however, caused overt maternal toxicity.

Biokinetic data showed that TAED is rapidly absorbed from the rat intestine and largely metabolized via diacetylation to TriAED and DAED which are excreted in the urine to more than 90% within 24 hours.

Skin penetration studies indicated, that 0.13%-4.3% of pure TAED or TAED present in solutions of detergent bases can penetrate rat skin depending on contact time.

Chronic toxicity, carcinogenicity, fertility and late stages of developmental toxicity (from birth to sexual maturity of offspring) have not been addressed. However, based on the chemical structure and the available toxicity and kinetic data it can be expected that TAED would cause no concern with respect to these endpoints.

There are only a few toxicity data available on DAED and they all indicate very low toxicity. There was no acute oral toxicity at 2000 mg DAED/kg BW and a NOEL of 5700 mg/kg BW/d has been reported in a 90-day rat feeding study. DAED was rapidly absorbed from the gastroinestinal tract and excreted via urine. It was non-mutagenic in the Ames test and non-sensitizing in the Magnusson & Kligman test.
For all other endpoints, data on TAED can be used as bridging data because the physical chemical properties of both substances are very similar, TAED completely hydrolyzes to DAED in aqueous media within a few hours and TAED is largely metabolized to DAED in vivo, so that whenever examining TAED in vitro or in vivo, DAED is evaluated as well.

As relevant consumer contact scenarios the direct contact during handwashing of fabrics, the contact with clothes containing product and the ingestion of product because of residues on dishware were identified. Also, inhalation of dust formed during handling of detergents was considered.
Assessment of these scenarios revealed only very minor consumer exposure to TAED and DAED, 0.013 and 0.089 µg/kg BW/d, respectively. In conjunction with the low toxicity of both substances, there is no hazard and no risk for human health from TAED and DAED during foreseeable use of the consumer products considered in this risk assessment.

Only accidental contact or misuse may lead to significant exposure. However, due to the fact that TAED and DAED possess a very low acute toxicity and are practically non-irritating to eyes, even these scenarios do not cause concern.

6. References

AISE (1992) Principles for Environmental Risk Assessment of Detergent Chemicals in Europe; Outcome of 2nd AISE Workshop , Limelette, October 1992.

AISE (2002). TAED: Compilation of used tonnage in household detergents in year 2000, 2002-05-24 Buecking, H.W., Reinhardt, D., Lötsch, R., Ziemer, M., Pleschke, H. (1990). Environmental behaviour and testing of the biodegradation of bleach systems, Comun. Jorn. Com. Esp. Deterg. 21: 167-82, ISSN 0212-7466

AISE (2002a). Personal Communication. Mail of 23 May 2002.

AISE (2002b). Table of habits and practices for consumer products in Western Europe, March 2002.

Bauknecht GmbH (2002). Zentralverband der Elektro- und Elektronikindustrie, Frankfurt/Main, Germany. Personal communication.

Carthew P. Personal communication (2001). Mail of 23 July 2001.

CCR GmbH & Co. KG on behalf of Hoechst AG – Kastengrund (1988). Salmonella typhimurium and Escherichia coli reverse mutation assay with TAED. Unpublished data. Project No. 138903.

CCR GmbH & Co. KG on behalf of Hoechst AG – Kastengrund (1989). Chromosome aberration assay in Chinese hamster V79 cells in vitro with TAED. Unpublished data. Project No. 1147205.

Clariant AG – Surfactants Division (1999). The clean and clever way of bleaching. Marketing brochure.

Clariant GmbH (2002). Diacetyl ethylene diamine (DAED) - Water solubility. Clariant GmbH Division Functional Chemical, RQA-Analytics/Biology, Report No. H575.

Clariant (2002a). Clariant GmbH, Division FUN: Tetracetylethylenediamine (TAED) – Perhydrolysis and Hydrolysis Study, Report No. H 563, 2002-05-28

Clariant (2002b). Clariant, Lancaster 2002-3, Catalogue on Research Chemicals, www.lancastersynthesis.com, page 547, Order No. 8645

Cramer J (2001). Personal communication. Mail of 01 August 2001.

ECETOC (2001). Peracetic acid (Cas No. 79-21-0) and its equilibrium solutions. JACC report no. 40.

ECETOC (2001a). Joint Assessment of Commodity Chemicals (JACC) Reports No. 40, Peracetic Acid, CAS No. 79-21-0, ISSN-0733-6339-40

EU (1996). EU Technical Guidance Document Risk Assessment New Notified and Existing Substances, ISBN 92-827-8012-0

EU (2002). Draft Revised EU Technical Guidance Document Risk Assessment New Notified and Existing Substances, May 2002

EUSES TAED/DAED (2002). EUSES Assessment for TAED and DAED, 2002

EUSES (1997). European Union System for the Evaluation of Substances, Software version 1.00

Gilbert PA (1992). TAED – Tetraethylenediamine. In: Hutzinger O (ed). The handbook of environmental chemistry. Springer-Verlag Berlin Heidelberg, Volume 3 Part F p. 319-328.

Henkel KGaA (2002a). Internal data. Mail of 24 May 2002.

Henkel KGaA (2002b). Internal data. Mail of 24 May 2002.

Henkel KGaA – ZR-FE/Toxikologie (1980a). Tetraacetylethylendiamin (TAED) – toxikologische Prüfungen. Unpublished data. Report No. 733.

Henkel KGaA – ZR-FE/Toxikologie (1980b). Pathologisch-anatomische und pathologisch-histologische Untersuchung zur Prüfung der Inhalations-Toxizität von TAED. Unpublished data. Report No. 53.

Henkel KGaA – Institut für Toxikologie (1984). N,N,N',N'-Tetraacetylethylendiamin (TAED) – Prüfung auf Mutagenität im Mikrokern-Test in vivo. Unpublished data. Archive No. 840122.

Henkel KGaA – Institut für Toxikologie (1987). Tetra-acetyl-ethylen-diamin – 90-Tage-Test mit wiederholter oraler Verabreichung an Ratten. Unpublished data. Archive No. 860114.

Henkel (1972a). Henkel KGaA, TAED – Closed Bottle Test, OECD 301D, Report No. 0000749

Henkel (1972b). Henkel KGaA, DAED – Closed Bottle Test, OECD 301D, Report No. 1491

Henkel (1972c). Henkel KGaA, TAED – Modified OECD Screening Test, OECD 301E, Report No. 0000747

Henkel (1972d). Henkel KGaA, TAED – Acute Fish Toxicity, DIN 38421, part 15, Report No. 0000750

Henkel (1972e). Henkel KGaA, DAED – Acute Fish Toxicity, DIN 38421, part 15, Report No. 2675

Henkel (1972f). Henkel KGaA, TAED – Acute Daphnia Toxicity, DIN 38421, part 11, Report No. 0000751

Henkel (1972g). Henkel KGaA, DAED – Acute Daphnia Toxicity, DIN 38421, part 11, Report No. 2675

HERA (2002). Human and environmental risk assessment on ingredients of European household cleaning products. Guidance methodology document.

HERA (2001). HERA - Guidance Document Methodology, June 2001

Hirschen M and Meuth H (2002). Tetra acetyl ethylene diamine (TAED) – Perhydrolysis and hydrolysis study. Clariant GmbH Division Functional Chemical, RQA-Analytics/Biology, Report No. H563.

HMR Deutschland GmbH – ProTox (1999). TAED - Testing for acute oral toxicity in the male and female Wistar rat. Unpublished data. Report No. 99.0452.

Hoechst (1970). ETAD Fermentation Tube Method (anaerobic bacteria), Report No. 08.04.1970

Hoechst (1983). OECD 302B, Zahn-Wellens-Test, Report No. W 83-016, 1983

Hoechst (1985). OECD 203, Acute Fish Toxicity (Danio rerio), Test report No. 85.0056

Hoechst AG- Pharma Forschung Toxikologie (1986a). TAED - Testing for acute oral toxicity in the male and female Wistar rat. Unpublished data. Report No. 86.1413.

Hoechst AG – Pharma Forschung Toxikologie (1986b). Hoe S 3711 – Test for primary dermal irritation in the rabbit. Unpublished data. Report No. 86.1355.

Hoechst AG - Pharma Forschung Toxikologie (1986c). TAED – Test for primary eye irritation in the rabbit. Unpublished data. Report No. 86.1356.

Hoechst (1992). OECD 209, Activated Sludge, Respriration Inhibition Test, Report No. 92-0129-01

Hoechst AG - Pharma Development, Central Toxicology (1993a). TAED – Test for primary dermal irritation in the rabbit. Unpublished data. Report No. 93.0071.

Hoechst AG – Pharma Development, Central Toxicology (1993b). TAED - Testing for primary eye irritation in the rabbit. Unpublished data. Report No. 93.0070.

Hoechst (1995a). OECD 301B, Sturm CO2 Evolution Test, Test report No. B 812b

Hoechst (1995b). OECD 303A, Coupled Units Test, Test report No. B 812a, 1995

IUCLID Clariant (2002)

Klimisch H-J, Andreae M and Tillmann U (1997). A systemic appraoch for evaluating quality of experimental toxicological and ecotoxicological data. Reg. Tox. Pharmacol. 25: 1-5.

Martin Davies D And Deary ME (1991). Kinetics of the hydrolysis and perhydrolysis of tetraacetylethylenediamine, a peroxide bleach activator. J. Chem. Soc. Perkin Trans. 2: 1549-1552.

Moran G (2002). Data quality of Unilever data on TAED. Mail of 03 May 2002.

Official publication of the French legislation ("Journal Officiel de la Republique Francaise") concerning substances used in dish care products which may come in contact with foods, 1990.

Procter & Gamble (2002). TAED – Summary on internal biodegradation and acute ecotoxicity data

RBM on behalf of Hoechst AG – Pharma Research Toxicology and Pathology (1994). TAED – Teratogenesis study in rats by oral route. Unpublished data. Exp. No. 920887.

RCC AG on behalf of Hoechst AG - Pharma Forschung Toxikologie und Pathologie (1989). Subacute 28-day oral toxicity (gavage) study with TAED in the rat. Unpublished data. Project No. 233820.

Reinhardt, G., Schuler, W., Quack, J. (1989). TAED - manufacture, effects and environmental properties, Comun. Jorn. Com. Esp. Deterg., 20: 165-179

Safepharm Laboratories Limited on behalf of Warwick International Limited (1982a). Toxicity, irritancy and sensitisation studies on T.A.E.D.: Determination of the acute oral median lethal dose (LD50) of T.A.E.D. in the rat, exp. no. 558/8203. Unpublished data.

Safepharm Laboratories Limited on behalf of Warwick International Limited (1982b). Toxicity, irritancy and sensitisation studies on T.A.E.D.: Federal register skin test: Determination of the degree of primary cutaneous irritation caused by T.A.E.D. in the rabbit, exp. no. 72/8204. Unpublished data.

Safepharm Laboratories Limited on behalf of Warwick International Limited (1982c). Toxicity, irritancy and sensitisation studies on T.A.E.D.: Federal register eye test: Determination of the degree of ocular irritation caused by T.A.E.D. in the rabbit eye, exp. no. 167/8204. Unpublished data.

Safepharm Laboratories Limited on behalf of Warwick International Limited (1982d). Toxicity, irritancy and sensitisation studies on T.A.E.D.: M&K miximization study determination of the contact sensitization potential of T.A.E.D. in the guinea pig, exp. no. 351/8203. Unpublished data.

Safepharm Laboratories Limited on behalf of Warwick International Limited (1982e). Ames test on T.A.E.D. Unpublished data. Report No. 1012/4/G.

Safepharm Laboratories Limited on behalf of Warwick International Limited (1995a). AR005: Chromosome aberration test in human lymphocytes in vitro. Unpublished data. Project No. 167/063.

Safepharm Laboratories Limited on behalf of Warwick International Limited (1995b). AR005: Micronucleus test in the mouse. Unpublished data. Project No. 167/064.

Schoeberl, P., Huber, L. (1988). Oekologisch relevante Daten von nichttensidischen Inhaltsstoffen in Wasch- und Reinigungsmitteln, Reports of HA Detergenzien

Schnuch A (2002). Personal communication. Mail of 26 February 2002.

Shell (2000). TAED: determination of soil sorption coefficient (K_{oc}), Report No. CSC 00349

SRC BCF (1999). Syracuse Research Corporation, Estimation program BCF, version 2.12

SRC Henry (1999). Syracuse Research Corporation, Estimation program Henry, version 3.02

SRC Hydro (1999). Syracuse Research Corporation, Estimation program Hydro, version 1.67

SRC KOWWin (1999). Syracuse Research Corporation, Estimation program KOWWin, version 1.63

SRC MPBPWin (1999). Syracuse Research Corporation, Estimation program MPBPWin, version 1.31

SRC PCKOC (1999). Syracuse Research Corporation, Estimation program PCKOC, version 1.66

SRC WSKOW (1999). Syracuse Research Corporation, Estimation program WSKOW, version 1.33

TGD, Technical guidance document in support of Commission directive 93/67/EEC on risk assessment for new notified substances and commission regulation (EC) no. 1488/94 on risk assessment for existing substances, Parte I (1996). Appendices IV-VI.

TherImmune Research Corporation on behalf of Warwick International Limited (2000a). 90-day oral toxicity of tetraacetylethylenediamine (TAED) in Sprague-Dawley rats (OPPTS 870.3100). TherImmune study number 1152-102. In: Mitchell M (2001). TAED - Robust study summary screening information data sets (SIDS) – health effects. Warwick International Limited, unpublished confidential data, dated 17 September 2001 and amended by Elsmore R, mail of 14 March 2002.

TherImmune Research Corporation on behalf of Warwick International Limited (2000b). 90-day dermal toxicity of tetraacetylethylenediamine (TAED) in Sprague-Dawley rats (OPPTS 870.3250). TherImmune Reserach Corporation, study number 1152-103, dated Oct. 20th, 2000.

Toxikon Corporation on behalf of Warwick International Limited (2000a). Acute oral toxicity test – OECD. Toxikon final report 00-4424-G2, dated Oct. 18th 2000.

Toxikon Corporation on behalf of Warwick International Limited (2000b). Salmonella typhimurium and Escherichia coli reverse mutation assay – ICH. Toxikon final report 00-4424-G1, dated Oct. 23rd 2000.

Tucker, J. (1935). Amer.Chem.Soc, 1935: 1989 cited in Beilstein Online 2002, BRN 1762220

Unilever Research Colworth (1975). TAED - Magnusson and Kligman sensitization test in guinea pigs. Unpublished data. Study reference SSM 75.30.

Unilever's Toxicology Lab (1968). Tetra acetyl ethylene diamine (TAED): Acute oral toxicity in mice – summary of study no. 68.388. In: SEAC Toxicology Group - Unilever Research

Colworth (2001). Tetra acetyl ethylene diamine (TAED): Toxicity and ADME summary data. Unpublished data. Document reference D01-023.

Unilever's Toxicology Lab (1976). Tetra acetyl ethylene diamine (TAED): Acute oral toxicity in rats – summary of study no. RG 963. In: SEAC Toxicology Group - Unilever Research Colworth (2001). Tetra acetyl ethylene diamine (TAED): Toxicity and ADME summary data. Unpublished data. Document reference D01-023.

Unilever's Toxicology Lab (1978a). Tetra acetyl ethylene diamine (TAED): Oral absorptioin, metabolism and excretion study in rats – summary of study no. AM77.01 (report no. P CE 78 1147). In: SEAC Toxicology Group - Unilever Research Colworth (2001). Tetra acetyl ethylene diamine (TAED): Toxicity and ADME summary data. Unpublished data. Document reference D01-023.

Unilever's Toxicology Lab (1978b). Tetra acetyl ethylene diamine (TAED): Skin penetration study in rats – summary of study no. AM77.01 (report no. P CW 78 1147). In: SEAC Toxicology Group - Unilever Research Colworth (2001). Tetra acetyl ethylene diamine (TAED): Toxicity and ADME summary data. Unpublished data. Document reference D01-023.

Unilever (1979). TAED – Acute Ecotoxicity studies on Carassius auratus, Daphnia magna, Gammarus pulex and Chlorella vulgaris, Study Report D87038/D02-035

Unilever's Toxicology Lab (1980). Tetra acetyl ethylene diamine (TAED): Acute inhalation toxicity study in rats – summary of study no. R1220 (IT80.001). In: SEAC Toxicology Group - Unilever Research Colworth (2001). Tetra acetyl ethylene diamine (TAED): Toxicity and ADME summary data. Unpublished data. Document reference D01-023.

Unilever's Toxicology Lab (1981). Tetra acetyl ethylene diamine (TAED): 13-week inhalation toxicity study in rats – summary of study no. R1234 (IT80.004). In: SEAC Toxicology Group - Unilever Research Colworth (2001). Tetra acetyl ethylene diamine (TAED): Toxicity and ADME summary data. Unpublished data. Document reference D01-023.

Unilever (1981a). TAED – Ready biodegradability, Sturm Test, Study Report D87038

Unilever (1981b). TAED – River die-away tests with radiolabelled TAED (14-C acetyl & 14-C-ethylene), Study report D87038

van de Plassche et al. (1999). Moret Ernst & Young Management Consultants (second draft). Rep. No. 601503013, p. 1-64, Nov. 1999.

Vermeire TG, van der Poel P, van de Laar RTH and Roelfzema H (1993). Estimation of consumer exposure to chemicals: Application of simple models. Sci. Total Env. 136: 155-176.

Warwick (1989). OECD 301E, Modified OECD Screening Test, Warwick Ltd, Rep. No. 89/WCT002/0648

Warwick (1992). Determination of Kow for TAED and DAED, Report No.TR 92023

Warwick (2000a). Tetracetylethylenediamine (TAED) – Determination of the n-Octanol/Water Partition Coefficient according OPPTS 830.7550', GLP, Springborn Laboratories Inc., Study No. 13727.6100, 2000-06-09

Warwick (2000b). Tetraacetylethylenediamine (TAED) – Acute Toxicity to Rainbow Trout (Oncorhnchus mykiss) under flow through conditions, Study Report No. WI/SLI/001, June 7, 2000

ZVEI and IKW (1999). Untersuchung und Bewertung der Hautverträglichkeit moderner Haushaltswaschverfahren. Industrieverband Körperpflege- und Waschmittel e.V. und Zentralverband der Elektro- und Elektronikindustrie, Frankfurt/Main, March 1999.

7. Contributors

This report was developed by exerts from the following companies:
Caffaro, Clariant (Lead & Report), Henkel, Unilever, P&G and Warwick, with the assistance of the members of the HERA Environmental Task Force and the HERA Human Health Task Force.