Hydrolysis of chemicals as a function of structure and pH: Meeting the information requirements of REACH in a reliable way and opportunities for product innovation

Wissenschaftliche Arbeit

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Fachökotoxikolge (GDCh/SETAC GLB)

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Hiermit bestätige ich, dass das vorgeschlagene Thema nicht Bestandteil meiner Routinearbeit beim Arbeitgeber bzw. Doktorarbeit oder laufenden Tätigkeit ist.

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Professor Dr. Andreas Schäffer, Institut für Umweltwissenschaften (Biologie V) der RWTH Aachen, danke ich für seine Gutachtertätigkeit.
Mein Dank gilt zudem der BASF SE für die finanzielle Förderung meiner Ausbildung zum Fachökotoxikologen (GDCh/SETAC GLB).

Today's problems come from yesterday's solutions.
Peter M. Senge

Nie werde ich den Moment vergessen, als wir uns 2001 in Stockholm trafen, um dort über eine Konvention zu verhandeln, in der es um völkerrechtlich bindende Verbots- und Beschränkungsmaßnahmen für bestimmte Schadstoffe ging, also um Pestizide wie DDT, Hexachlorbenzol oder Dioxine oder Furane. Diese „Persistant Organic Pollutants" (POPs) werden auch als das „Dirty Dozen" der chemikalischen Stoffe bezeichnet. Gerade in dem Augenblick, als in Stockholm diese Konvention von Delegierten aus 122 Staaten in einer feierlichen Zeremonie unterschrieben wurde, wies jemand darauf hin, dass 1948, genau in diesem Saal, der Schweizer Chemiker Paul Hermann Müller für seine Entdeckung der DDT-Wirksamkeit den Nobelpreis für Medizin bekommen habe. Vor rund sechzig Jahren war ein Mensch für seine Forschungen zu DDT ausgezeichnet worden, und nun stand dieses Pestizid auf einer Liste der umweltschädlichen Stoffe. Für mich war das ein Zeichen großer Offenheit und Toleranz in der Wissenschaft. Da wurde ein Stillstehen genutzt, um sich selbst in Frage zu stellen.
Klaus Töpfer

Everything should be made as simple as possible, but not simpler.
Albert Einstein

Contents

Abbreviations and Symbols

Abbreviations

ACS	American Chemical Society
EC	European Communities
EPA	Environmental Protection Agency
FEMS	Federation of European Microbiological Societies
NHFG	No hydrolysable functional groups
NLFG	No labile functional groups
OECD	Organization for Economic Cooperation and Development
PBT	Persistent, bioaccumulative and toxic; Polybutyleneterephthalate
REACH	Regulation (EC) 1907/2006 of the European Parilament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemicals
QSA(P)R	Quantitative Structure-Activity (Property) Relationship
SA(P)R	Structure-Activity (Property) Relationship
SETAC	Society of Environmental Toxicology and Chemistry
vPvB	Very persistent and very bioaccumulative

Symbols

BCF	Bioconcentration Factor	$L\ kg^{-1}$
$D_{0.5\ B}$	Half-life for biodegradatation	d, h
$D_{0.5\ H}$	Half-life for hydrolysis	d, h
$D_{0.5\ P}$	Half-life for photodegradation	d, h
DOC	Dissolved organic carbon	$mg\ L^{-1}$
EC_X	Effect concentration measured as X%	$mg\ L^{-1}$
H	Henry's law constant	$Pa\ m^3\ mol^{-1}$
k_a,k_b	Specific acid, base rate constant	$L\ mol^{-1}\ h^{-1}$
K_d	Distribution coefficient	$L\ kg^{-1}$
K_{OC}	Organic carbon-normalised distribution coefficient	$L\ kg^{-1}$
k_n	Neutral rate constant	h^{-1}
k_{obs}	Total hydrolysis rate constant	h^{-1}
K_{OW}	Octanol-water partition coefficient	-
LC_X	Lethal concentration measured as X%	$mg\ L^{-1}$
M	Molar mass	$g\ mol^{-1}$
$^1O_2$	Singulett oxygen	-
P_V	Vapour pressure	Pa
R	Organic residue in a molecule	-
RX	Hydrolysable organic molecule	-
S_W	Water solubility	$mg\ L^{-1}$, $mol\ L^{-1}$
$ThCO_2$	Theoretical CO_2 formed per test substance	$mg\ mg^{-1}$, %
ThO_2	Theoretical O_2 consumed per test substance	$mg\ mg^{-1}$, %
X	Leaving group in a molecule; Percentage of a testpopulation	- %

1 Introduction

1.1 The water phase

Water is an ubiquitous natural resource in the environment and the hydrosphere covers about 71% of the earth's surface which is equivalent to $510 \cdot 10^6$ km^2 (Schüürmann et al. 2007). Soil and air usually contain significant amounts of water which is also the major constituent of biological cells. Chemicals released into the environment are thus very likely to encounter water, and the question is if, in what way and how fast a chemical reaction with water will occur (Schüürmann et al. 2007).

1.2 Definition of hydrolysis

Hydrolysis can be defined as a chemical transformation process in which an organic molecule, RX, reacts with water, forming a new carbon-oxygen bond and cleaving a carbon-X bond in the original molecule according to figure 1 (Harris 1990, Hilal 2006, Sijm et al. 2007). X represents some leaving group (Schüürmann et al. 2007).

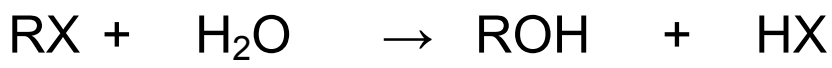

Figure 1: General hydrolysis reaction scheme.

Hydrolysis can occur as biotic (if catalysed by enzymes[1]) and abiotic reaction (if enzymes are not involved). Abiotic hydrolysis is likely one of the most common reactions of organic compounds with water in aqueous environments and thus a significant environmental fate process (Grayson 1986, Harris 1990, Reineke and Schlömann 2007). Abiotic hydrolysis reactions are commonly catalysed by hydrogen or hydroxide ions. Since the concentrations of hydrogen ion and

[1] The corresponding enzyme class is called hydrolases (Moss 2012). It is clearly the prevalent class of enzymes with respect to industrial applications (Fernandes 2010, Schäfer et al. 2007).

hydroxide ion change by definition with the pH of water, the rate of abiotic hydrolysis depends on the pH.
Under environmental conditions abiotic hydrolysis is considered relevant for halogenated aliphatics, organic acid esters, organic acid anhydrides, organophosphorous esters, epoxides, nitriles, carbamates and sulfonylureas (Larson and Weber 1994; Mabey and Mill 1978; Tinsley 2004; Wolfe and Jeffers 2000).
The focus of this work is – according to the above given definition - on abiotic hydrolysis.

1.3 Abiotic hydrolysis as part of environmental fate characteristics

Once a chemical has entered the environment it is i) transported, ii) distributed over various environmental compartments and eventually iii) transformed into other chemicals (Sijm et al. 2007). Transformation of a compound results in its disappearance from the environment by a change in chemical structure and can occur as biotic and abiotic processes. Important transformation processes are listed and briefly explained in table 1.

Table 1: Important biotic and abiotic transformation processes (Sijm et al. 2007).

Transformation process	Feature
Biotic	
Biodegradation[a]	Transformation by microorganisms
Biotransformation[a]	Transformation by other organisms
Abiotic	
Hydrolysis	Direct reaction of the chemical with water
Oxidation	Electron transfer from the chemical
Reduction	Electron transfer to the chemical
Photodegradation	Transformation due to interaction with (sun)light

[a] Biotic (i. e. enzyme catalyzed) hydrolysis reactions are part of these processes.

1.4 Regulatory background and relevance

In Europe important regulatory frameworks were established, e.g. the European Water Framework Directive, the European Soil Framework Directive, and recently, the European Regulation for Registration, Evaluation, Authorisation and Restriction of Chemicals (Schäffer et al. 2009). The latter is also known as REACH regulation and 'Hydrolysis as a function of pH' is one of its environmental fate information requirements (EC 2006). Since it is an Annex VIII requirement the corresponding substance information has to be available for all chemical substances manufactured or imported in quantities of 10 tonnes or more per year per manufacturer or importer (EC 2006). The relevant OECD guideline for the testing of chemicals is OECD111 (OECD 2004), in which the half-lifes for the abiotic hydrolysis of the test substance at 25 °C and pH-values of 4, 7 and 9 are determined. In addition products formed in an amount of 10% or above have to be considered (appendix 7.1). Abiotic hydrolysis products of a chemical substance may have a significant impact on its overall (eco)toxicity and environmental fate characteristics and have to be included in the environmental hazard – and risk assessment (Schäffer et al. 2009).

1.5 Goals

The goals of this work are:

i) to prepare unequivocal cut off-criteria for the decision if a hydrolysis study has to be performed to fulfill the information requirements of the REACH regulation;

ii) to compare the chemical structures of parent compound and hydrolysis products with respect to their impact on selected physical chemical -, environmental fate - and ecotoxicology data;

iii) to discuss opportunities for exploiting hydrolysis know how for product innovation.

2 Approach

2.1 Cut off-criteria for the decision on the necessity of a hydrolysis study

The description of the standard information required and specific rules for their adaption given in regulation (EC) 1907/2006 were used as a starting point. A precise definition of abiotic hydrolysis was taken from the scientific literature. Peer reviewed scientific publications were then systematically screened to identify i) substances having no hydrolysable functional groups at all, ii) substances having – under environmentally relevant conditions – exclusively very stable functional groups, iii) substances which are known to hydrolyse fast, iv) substances for which reliable hydrolysis rates/half-lifes are available or can be estimated with sufficient accuracy, v) substances being highly volatile.
On the basis of these findings and relevant test guidelines (e. g. OECD23 [OECD 2000] and OECD111 [OECD 2004]) unequivocal cut off-criteria for the decision if a hydrolysis study has to be performed were deduced and explained and possible benefits discussed.

2.2 Comparison of parent compound and hydrolysis products with respect to physical chemical -, environmental fate - and ecotoxicology data

The chemical structures of parent compound and hydrolysis products were analysed with respect to their impact on molar mass, water solubility, vapour pressure, octanol-water partition coefficient, distribution coefficient K_d, Henry's law constant, bioconcentration factor and effect concentrations. The scientific literature was checked for general trends deduced for these parameters.

2.3 Opportunities for product innovation

Opportunities for exploiting detailed know how on abiotic hydrolysis for the development of new and improved products were analysed with an emphasis on i) hydrolysis stability modification of the chemical itself, ii) hydrolysis stability modification of a precursor, matrix or capsule from which the chemical is to be

released. The scientific literature was systematically screened and different applications found and their benefits were briefly discussed.

3 Results and Discussion

3.1 Cut off-criteria for the decision on the necessity of a hydrolysis study

Following the approach described in chapter 2.1 unequivocal cut off-criteria were deduced. Most of them were already presented to and discussed with stakeholders of environmental sciences and regulation (Scholten 2010).
If the test substance fulfills at least one of the following criteria a hydrolysis study is suggested to be unnecessary.

3.1.1 Substance tonnage is below 10 tonnes per year

'Hydrolysis as a function of pH' is an Annex VIII data requirement of the REACH regulation. Information on the abiotic hydrolysis behavior has to be available for all chemical substances manufactured within or imported into the EU in quantities of 10 tonnes or more per year per manufacturer or importer (EC 2006). Hence, for substances with a tonnage below 10 t a^{-1} 'Hydrolysis as a function of pH' is not a standard information required.

3.1.2 Substance is readily biodegradable

According to Annex VIII, column 2 of the REACH regulation a study on hydrolysis as a function of pH 'does not need to be conducted if the substance is readily biodegradable'[2] (EC 2006). Hence, ready biodegradability is an official waiving argument.
The rationale behind this official waiving argument is obvious: For a substance being widely mineralized within ten days or even less in a ready biodegradability test the knowledge of precise half-lifes for abiotic hydrolysis is of minor relevance and thus dispensable.

[2] The precise wording would be 'readily biodegradable according to the OECD criteria'. This means that the substance was tested according to OECD 301 A to F or OECD 310 and the pass levels for DOC removal (70 %) or ThO_2/$ThCO_2$ (60%) were reached within a window of ten days (OECD 1992, OECD 2006).

3.1.3 Substance has a solubility in water below 0.1 mg L^{-1} under environmentally relevant conditions

Annex VIII, column 2 of the REACH regulation states that a study on Hydrolysis as a function of pH 'does not need to be conducted if the substance is highly insoluble in water' (EC 2006). However, no unequivocal cut off-criterion is given to differentiate between substances being highly insoluble and those being not. A solubility in water below 0.1 mg L^{-1} (Hollifield 1979) at 25°C and pH=7 is thus suggested to specify this official waiving argument.
The rationale behind this approach is therefore not at all scientific but regulatory to suggest a precise cut off-criterion for this official waiving argument.

3.1.4 Substance is inorganic

According to the scientific literature (e. g. Harris 1990, Hilal 2006, Sijm et al. 2007) hydrolysis can be defined as a chemical transformation process in which an organic molecule reacts with water, forming a new carbon-oxygen bond and cleaving a carbon-X bond in the original molecule (Figure 1). On the basis of this definition a hydrolysis study would not be required for inorganic substances.
The rationale behind this approach is to suggest a precise definition of abiotic hydrolysis and to have a clear differentiation from other processes (e. g. dissociation of a salt in water).

3.1.5 Substance has half-lifes at 25°C of above 1 year

This is the criterion for sufficiently stable substances given in OECD111 indicating that no further hydrolysis testing is required (OECD 2004). Substances with half-lifes at pH 4, 7 and 9 and 25°C definitely above one year are for example NHFG (no hydrolysable functional groups)- and NLFG (no labile functional groups)- compounds (Kollig et al. 1993, Wolfe and Jeffers 2000). Important categories of organic substances fulfilling these criteria are listed in table 2. The rationale of this official waiving argument is that abiotic hydrolysis is at best very slow under environmentally relevant conditions and thus of minor importance.

Table 2: Organic chemicals with half-lifes at pH 4 to 9 and 25°C above one year[a].

Organic substance category	**Source**
Alkanes	Harris 1990
Alkenes	Harris 1990
Alkynes	Harris 1990
Vinyl chloride[b]	Kollig et al. 1993, Mabey and Mill, 1978
Benzenes/Biphenyls	Harris 1990
Xylenes	Kollig et al. 1993, Wolfe and Jeffers 2000
Polycyclic aromatic hydrocarbons[c]	Harris 1990, Kollig et al. 1993
Halogenated aromatics/PCBs	Harris 1990, Mabey and Mill, 1978
Aromatic nitro compounds	Harris 1990, Kollig et al. 1993
Amines	Kollig et al. 1993
Aromatic amines	Harris 1990, Wolfe and Jeffers 2000
Alcohols	Harris 1990, Kollig et al. 1993
Phenols	Harris 1990
Glycols	Harris 1990
Nitriles	Mabey and Mill 1978
Ethers	Harris 1990, Kollig et al. 1993
Aldehydes	Harris 1990
Ketones	Harris 1990
Carboxylic acids	Harris 1990, Wolfe and Jeffers 2000
Sulfonic acids	Harris 1990

[a] Of course multifunctional organic substances in these categories may be hydrolytically reactive if they contain hydrolysable functional groups in addition to the listed functionality.

[b] and higher chlorinated derivatives.

[c] Homo- and heterocyclic species.

3.1.6 Substance has half-lifes at 25°C of below 24 hours

This criterion is from EC guideline C.7. (EC 1992). If the test substance is susceptible to such a fast abiotic hydrolysis at pH 4, 7 and 9 and 25°C the benefit of a precise half-life determination is very limited. Organic substances belonging to this group are for example Chloroacetylchloride (Brown et al. 2000) and Dimethylsulphate (Lee et al. 1980).

3.1.7 Measured half-lifes at 25°C are available

In those cases where reliable information on the half-lifes $D_{0.5\ H}$ at 25°C is available (e. g. in the reports of Ellington et al. 1987a, 1987b, 1988, Hilal 2006, Kollig et al. 1993 and Mabey and Mill 1979) it is suggested not to conduct a hydrolysis study but to use the available information instead. The rationale behind this waiving argument is to avoid unnecessary testing according to Annex XI, 1.1.2 of the REACH regulation.

3.1.8 Substance half-lifes at 25°C can be estimated with sufficient accuracy

For several classes of organic molecules values for acid, neutral and base rate constants (k_a, k_n and k_b) are available (e. g. in the reports of Ellington et al. 1987a, 1987b, 1988, Hilal 2006, Kollig et al. 1993 and Mabey and Mill 1979). These values can be used to estimate the total hydrolysis rate constant k_{obs} for a given pH and finally the corresponding half-life $D_{0.5\ H}$ (for details see Appendix 7.2). If the raw data are reliable and the resulting half-life estimation is clearly fulfilling criterion 3.1.5 or 3.1.6 a hydrolysis study is suggested to be unnecessary. In other cases the half-life $D_{0.5\ H}$ can often be estimated semi-quantitatively by comparison to substances for which hydrolysis data are available (Wolfe and Jeffers 2000). The approach consists of i) description of reaction pathway, ii) literature search for hydrolysis rate constants for this or a similar class of compounds, iii) rate constant estimation by interpolation (Kollig et al. 1993, Wolfe and Jeffers 2000).

3.1.9 Substance has a Henry's law constant of above 100 Pa m^3 mol^{-1}

The Henry's law constant H is a measure of the potential for a substance to be lost from solution by evaporation (OECD 2000). If H is greater than 100 Pa m^3 mol^{-1} more than 50% of the substance could be lost from the water phase in 3-4 hours (Mackay 1992). The rationale behind this criterion is that for substances with sufficiently high H-values the water phase is not the compartment of concern and atmospheric transformation processes become much more relevant. In these cases a hydrolysis study is suggensted to be not necessary. The approach to define a threshold value for the Henry's law constant was successfully transferred to adapt the set-up of the activated sludge respiration inhibition test for volatile substances (Scholten and Schwarz 2011).

3.1.10 Concluding remarks

Profound information on the REACH endpoint 'Hydrolysis as a function of pH' is available in great amount. In many cases it is therefore possible to meet the corresponding information requirements of the REACH regulation in a reliable way without performing a hydrolysis study.

Most of the suggested cut off-criteria were presented and discussed with stakeholders of environmental sciences and regulation (Scholten 2010). In a rough estimation a coverage of >80% was determined. Hence, for more than 80 % of the REACH substances a hydrolysis study is – according to the cut of-criteria suggested in this work – unnecessary and could be avoided. Given a total number of pre-registered substances of above 130,000 (Daginnus 2009, Öberg and Iqbal 2012) this is a significant total number of hydrolysis studies which could be avoided.

The resulting benefits would be i) reduction of emissions due to e. g. savings of consumables, chemicals and energy and reduced demand for technical equipment, ii) savings of time, laboratory capacity and cost.

3.2 Comparison of parent compound and hydrolysis products with respect to physical chemical -, environmental fate - and ecotoxicology data

3.2.1 Introduction

During a hydrolysis reaction the parent compound RX is converted into the reaction products ROH and HX (figure 1). Differences between parent compound and hydrolysis products with respect to their impact on selected parameters are summarized in table 3 and briefly explained afterwards.

Table 3: Differences between parent compound and hydrolysis products.

Parameter	Effect[a]	Reference
Molar mass	↓[b]	-
Water solubility	↑	Schüürmann et al. 2007, Sijm et al. 2007
Vapour pressure	0	Schüürmann et al. 2007
Octanol-water partition coefficient	↓	Sijm et al. 2007
Distribution coefficient	0	Schüürmann et al. 2007
Henry's law constant	0	Schüürmann et al. 2007
Bioconcentration factor	0	Schüürmann et al. 2007; Sijm et al. 2007
Half-life for photodegradation	0	Sijm et al. 2007
Half-life for hydrolysis	↑	-
Half-life for biodegradation	-	Reineke and Schlömann 2007, Schüürmann et al. 2007; Sijm et al. 2007
Effect concentration	↑	Reineke and Schlömann 2007, Sijm et al. 2007

[a] ↓ generally/mostly lower for products; ↑ generally/mostly higher for products; 0 no general trend found.

[b] Hydrolysis products generally have lower molar masses than the parent compound. However, during hydrolysis of an amide with a terminal amino group NH_2 (16 g mol^{-1}) is substituted by OH (17 g mol^{-1}) resulting in a higher molar mass of the alcohol formed.

3.2.2 Molar mass

Molar mass, M, is the mass per substance amount and mostly quoted in g mol^{-1}. Hydrolysis products generally have lower molar masses than the parent compound – except for the alcohol formed upon hydrolysis of an amide with a terminal amino group (table 3).

3.2.3 Water solubility

Water solubility, S_W, of a compound is the highest equilibrium concentration it can achieve as dissolved species in an aqueous solution. Typical units of S_W are mol L^{-1} and mg L^{-1} (Schüürmann et al. 2007). Cleavage of a C-X bond and introduction of a hydroxyl group during a hydrolysis reaction generally result in formation of polar products which are more water soluble and less lipophilic than the parent compound (Sijm et al. 2007).

3.2.4 Vapour pressure

Vapour pressure, P_V, is the pressure of the pure chemical vapour that is in thermodynamic equilibrium with the pure chemical in its solid or liquid state. P_V thus characterizes the extent to which the chemical evaporates from its pure phase into air (Schüürmann et al. 2007) and is mostly quoted in Pa. As a general rule P_V increases with decreasing molecular size which is explained with decreasing strength of van der Waals interactions (Schüürmann et al. 2007). However, other effects result in increased attractive strengths between the hydrolysis product molecules – some of them are charged under environmental conditions. As a consequence, no general trend for P_V was found in the literature.

3.2.5 Octanol-water partition coefficient

Octanol-water partition coefficient, K_{OW}, is defined as ratio of the equilibrium concentrations in n-octanol and water and is as such dimensionless (Schüürmann et al. 2007). The logarithm of K_{OW} (i. e. log K_{OW}) is used as an indication of a chemical's propensity for bioconcentration by aquatic organisms (van Leeuwen 2007). Both higher water solubility and lower lipophilicity of the

hydrolysis products contribute to a K_{OW} being lower than K_{OW} of the parent compound.

3.2.6 Distribution coefficient

Distribution coefficient, K_d, is defined as the ratio of equilibrium concentrations of a dissolved test substance in a two phase system consisting of a sorbent and an aqueous phase (OECD 2001). Often the concentrations are given on a weight/weight base for the solid phase and on a weight/volume base for the aqueous phase. Hence, a typical unit of K_d is L kg^{-1} (Schüürmann et al. 2007). The physical meaning of this dimension can be interpreted as “the volume of water (in liters) containing that amount of the chemical which is equal to the amount present in 1 kg solid material” (Sijm et al. 2007). Different types of forces contribute to the association of compounds with solids (Schüürmann et al. 2007). Some of them are expected to be stronger (hydrogen bonding) and others are expected to be weaker (van der Waals interactions) for hydrolysis products in comparison to the parent compound. Consequently, no general trend was found in the literature.

3.2.7 Henry’s law constant

Henry’s law constant, H, is the ratio of the partial pressure above a dilute solution due to solute and its concentration in solution (Schüürmann et al. 2007). H is often quoted in Pa m^3 mol^{-1} and usually derived from the ratio of P_V and S_W of the pure compound (Schüürmann et al. 2007, Sijm et al. 2007). For P_V of parent compound and hydrolysis products no general trend was found, S_W-values of the hydrolysis products are generally higher than those of the parent compound (see above). For the Henry’s law constant a general trend was not found in the literature.

3.2.8 Bioconcentration factor

Bioconcentration factor, BCF, is defined as the ratio of steady-state concentrations of the compound in/on the organism or specified tissues thereof and the surrounding medium (OECD 2010). BCF is thus expressed in L kg^{-1}. Parameters affecting the BCF of a substance are i) number of Hydrogen bond donors, ii) number of Hydrogen bond acceptors, iii) molecular weight, iv) log Kow (Proudfoot et al. 2005, Sijm et al. 2007, Vieth et al. 2004, Wenlock et al. 2003). Also v) ionization, vi) molecular size, vii) water solubility and viii) metabolism have to be taken into account (De Wolf et al. 1992, 2007, Dimitrov et al. 2003, 2005a, 2005b, 2012, Opperhuizen et al. 1985). In addition, some of the parameters are related (ionization and water solubility, molecular weight and -size, etc.) and the logBCF=f(logKow)-curve has a maximum for narcotics (Dimitrov et al. 2003, 2005b). This complexity and the fact that some parameters are good arguments for higher BCFs of the hydrolysis products in comparison to the parent compound whereas others are arguments for the opposite do not allow to deduce a general rule on the relative BCFs of parent compound and hydrolysis products. Consequently, a general trend was not found in the scientific literature.

3.2.9 Photodegradation

Photodegradation can be defined as the sum of breakdown reactions of a chemical initiated by sunlight (van Leeuwen 2007). Either the reacting molecule itself directly absorbs light (direct photodegradation) or the molecule reacts with ions or radicals created by photolysis of other species (indirect photodegradation). In the aquatic compartment an important fraction of sunlight is absorbed by dissolved and particulate matter reducing the rates of direct photodegradation and changing the solar spectrum in deeper layers. Dissolved and particulate matter can also initiate indirect photoconversions (Sijm et al. 2007). Most relevant are indirect photolysis reactions with OH-radicals in the troposphere (Böhnhardt et al. 2008, Schüürmann et al. 2010) and with singlet oxygen $^1O_2$ in natural waters (Schüürmann et al. 2010). Given the complexity of both direct and

indirect photodegradation a general rule for the **half-lifes for photodegradation**, $D_{0.5\,P}$, of parent compound and hydrolysis products cannot be given.

3.2.10 Hydrolysis

Hydrolysis is defined in chapter 1.1. After cleavage of all hydrolysable carbon-X bonds and formation of the new carbon-oxygen bonds according to figure 1 hydrolysis is complete and no functional groups susceptible to hydrolysis are left. If two or more hydrolysable functional groups are available in the same molecule hydrolysis will be faster for the labile groups whereas more stable functional groups will hydrolyse more slowly. Hence, the **half-lifes for hydrolysis**, $D_{0.5\,H}$, of the hydrolysis products will - if at all - be higher than those of the parent compound.

3.2.11 Biodegradation

Biodegradation is the breakdown of a substance catalysed by enzymes (van Leeuwen 2007) either in the presence (aerobic) or in the absence of oxygen (anaerobic). General rules for the impact of the chemical structure on its biodegradability are given in the literature although exceptions exist (Boethling et al. 2007, Reineke and Schlömann 2007, Schüürmann et al. 2007, Sijm et al. 2007). For aliphatic hydrocarbons e. g. the following structural features are beneficial for biodegradation: linear C-chain, short chain length[3], chlorine more than six C-atoms from terminal C (Sijm et al. 2007). Carboxyl- and hydroxyl-groups tend to increase (aerobic) biodegradability of aliphatics and aromatics whereas nitro- and halogen-groups tend to decrease it (Reineke and Schlömann 2007, Schüürmann et al. 2007, Sijm et al. 2007). In addition, groups susceptible to (enzymatic) hydrolysis, chiefly esters and also amides, generally increase aerobic biodegradability (Boethling et al. 2007). An extensive list of substructures and their qualitative impact on biodegradability is given by Reineke and Schlömann 2007. Often hydrolysable functional groups are simultaneously

[3] The obvious mistake in the original reference (table 3.11 in Sijm et al. 2007) was corrected after discussion with and confirmation by the authors (Rorije 2012).

hydrolysed by both abiotic and biotic (i. e. enzyme catalyzed) reactions. The latter are part of the biodegradation process. Hence, the precise separation of abiotic hydrolysis and biodegradation is not possible. Consequently, a general rule on the relative **half-lifes for biodegradation**, $D_{0.5\,B}$, of parent compound and abiotic hydrolysis products is not given.

3.2.12 Effect concentration

Effect concentration, LC_X or EC_X, is the concentration affecting X% of a testpopulation after specified exposure time (van Leeuwen 2007). LC_X relates to lethality, EC_X relates to other effects (e. g. immobilization, growth rate). In most cases, hydrolysis is beneficial since less hazardous substances are formed (Reineke and Schlömann 2007, Sijm et al. 2007). Hence, LC_X– or EC_X-values of the hydrolysis products are mostly higher than those of the parent compound (table 3).

Very recently very promising results for the rational design of chemicals with low acute and chronic aquatic toxicity were published (Voutchkova et al. 2011, Voutchkova-Kostal et al. 2012). The authors suggest to use threshold values for logKow and ΔE (LUMO-HOMO gap) as design criteria to significantly increase the probability that the chemical will have low acute and chronic toxicity (Voutchkova et al. 2011, Voutchkova-Kostal et al. 2012).

3.2.13 Concluding remarks

Comparison of parent compound and hydrolysis products with respect to selected parameters revealed that general trends exist for molar mass and octanol-water partition coefficient (both being generally/mostly lower for the hydrolysis products) and water solubility, half-life for hydrolysis and acute effect concentrations (all being generally/mostly higher for the hydrolysis products). These trends and the specific exceptions are highly relevant when unnecessary negative effects on humans and/or the environment are to be avoided during the development of new chemicals already (see also chapter 3.3.2). These trends are also worth to be considered when the characteristics of parent compound

and its hydrolysis products are verified in detail to improve the overall efficiency of a process. An example is the simultaneous production and purification of dibutylsuccinate in a reactive distillation step and its subsequent hydrolysis (Bauduin et al. 2007). The more volatile reaction products are drawn off via the top of the column to achieve full conversion of the esterification. Due to its limited water solubility the hydrolysis product n-butanol can be widely recycled by simple phase separation. Both features are essential for a highly efficient process.
The resulting benefits are i) quantitative reduction of emissions due to e. g. savings of raw materials and energy and a lean production plant, ii) the resulting cost savings.

3.3 Opportunities for product innovation

3.3.1 Introduction

The idea of exploiting hydrolysis know how for product innovation (i. e. design and development of new or improved chemical substances) is not new. Current reviews are available (e. g. Engineer et al. 2011, Lundberg et al. 2008) and the described research activities can be classified into two groups: i) the hydrolysis stability of the chemical itself is modified, ii) the hydrolysis stability of a precursor, matrix or capsule is modified from which the chemical is to be released.

3.3.2 Hydrolysis stability modification of the chemical itself

Several studies exist in the scientific literature pursuing the objective **to enhance the hydrolytic stability** of a substance or substance class itself. Gerasov et al. 2011 have investigated the structural criteria affecting the stability of dioxaborine dyes against alkaline hydrolysis since improved stability is needed for additional practical applications of these dyes. De Gooijer et al. 2003 have developed PBT (polybuthyleneterephthalate) granules with significantly enhanced hydrolytic stability by reducing the carboxylic end group concentration. The improved PBT is a superior material for optical fiber tubing. Wei and Fang 2011 have synthesized novel sulfonated polyimide ionomers with increased hydrolytic stability as improved key components of proton exchange membrane fuel cells. The above mentioned studies have in common that expert know how on abiotic hydrolysis was used to rationally develop new or modified products with enhanced hydrolysis stability and by this superior technical performance.
Other research groups have focused on **reducing the (hydrolytic) stability** of a substance or substance class. Lundberg et al. 2008 and Tehrani-Bagha and Holmberg 2007 state that there is a growing demand for cleavable surfactants. Most of them contain a hydrolysable bond breaking down after a change of pH. The major driving force behind current interest in these surfactants are environmental concerns (i. e. improved rate of biodegradation and reduced aquatic toxicity) according to the regulations adopted by the European Union

(Lundberg et al. 2008, Tehrani-Bagha and Holmberg 2007). However, there are also other reasons for the development of cleavable surfactants: i) to avoid unwanted effects (foaming, formation of emulsions) in subsequent process steps, ii) to have a cleavage product impart a new function (skin care). Rieger et al. 2002 present an interdisciplinary approach to develop environmentally benign chemicals which are not persistent in the environment. The authors argue for applying the design of safer chemicals already during the conceptual and development phases of new chemicals. Different safe textile auxiliaries being biodegradable and maintaining good technical performance are presented: i) ethoxylated hydroxybiphenyls as dispersing agents (Meier et al. 2000), ii) iminodisuccinate (Reineke et al. 2000) and ethyleneglycoldicitrate (Reineke and Schlömann 2007) as sequestering agents, iii) alkylphosphates linked to polyethyleneglycol and ethoxylated amine as levelling agents (Heinen et al. 2000). The chemical structures of ethyleneglycoldicitrate and the phosphatetriester show that rational introduction of weak links by hydrolysable bonds is a good approach to improve biodegradability and to maintain good technical performance (Rieger et al. 2002).

3.3.3 Hydrolysis stability modification of a precursor, matrix or capsule

Precursors with ester functionalities are an attractive option to increase the oral availability of therapeutics that were otherwise orally unavailable (Testa and Mayer 2003). Bender et al. 2008 have recently shown that cyclopropane-carboxylic acid esters as prodrugs can provide significantly increased stability in the acidic environment of the stomach and under the alkaline conditions of the intestine. The benefit should be an improved absorption of the intact prodrug into the plasma. Enhanced hydrolysis stability is explained with unique properties of the cyclopropyl group (Bender et al. 2008). Hence, this is another example for expert know how on abiotic hydrolysis which was used to rationally develop an innovative product with superior performance.

Another field of research is **matrices or capsules** made from biodegradable polymers as controlled release or delivery systems (Ikada and Tsuji 2000). The

polymers contain hydrolysable bonds making them more prone to degradation via abiotic and enzymatic hydrolysis (Engineer et al. 2011). Hennink and Van Dijk-Wolthuis 2003 have developed a hydrogel in which two types of polymers are linked by hydrolysable spacers. Upon hydrolysis of the hydrogel substance release occurs. Van Koppenhagen et al 2003 describe microcapsules containing cross-linking agents with hydrolysable ester bonds as key feature. Under basic conditions hydrolysis of these bonds occurs resulting in substance release. Major applications of this technology are the controlled release of pesticides and other agrochemicals (Van Koppenhagen et al. 2003).
McCoy et al 2007 suggest to combine the two approaches described before: Polymerizable ester drug conjugates were synthesized and copolymerized into biomaterials. Incorporation of neighboring group moieties with different chemical structures allowed to rationally control the rate of ester hydrolysis (and hence drug liberation) in a wide range. The authors consider their results to be essential for the development of tailored release materials since release rates can be controlled by molecular structure (McCoy et al. 2007).

3.3.4 Concluding remarks

Two major objectives were found in the scientific literature: i) abiotic hydrolysis stability of the active chemical substance is adjusted (enhanced or reduced), ii) its release is to be controlled in space and/or time.
In those cases where chemicals with enhanced hydrolysis stability are developed the resulting benefits are i) additional applications and/or ii) improved service life.
Another and more general aspect of adjusting the hydrolysis stability of a chemical substance is to have the stability required and the half-life in the environment well-balanced. It does not make sense if e. g. the constituent of a detergent which has to be stable and active in a washing machine for just two hours has a half-life in the environment of 1000 a! Avoidance of unnecessary persistence - and of course other unnecessary negative effects on humans and/or the environment - should thus be an important factor during chemical product design and development already (Boethling et al. 2007, Papa and

Gramatica 2010, Voutchkova et al. 2010). This would be a clear step forward towards inherently safe chemicals and green chemistry (Voutchkova et al. 2010, Anastas 2012). Resulting benefits are: i) qualitative emission reduction, ii) less strict classification and labeling (and thus lower water endangerment class) of the substances (Steinhäuser et al. 2005), iii) reduced study requirements[4], iv) reduced information requirements in the registration dossier, v) lower technical safety requirements on the sites and – due to the latter three issues – vi) significant cost savings.

Controlled release or delivery of the active chemical substance from a hydrolysable precursor, matrix or capsule is used to obtain higher substance concentrations at the target location or to maintain effective substance concentrations for a longer time with just one dosing. In both cases improved efficiency results since a lower amount of substance is needed to achieve a certain effect. The resulting benefits are: i) quantitative reduction of emissions due to reduced substance release into man and/or environment, savings of raw materials, consumables, chemicals and energy, ii) the resulting cost savings.

[4] If a chemical substance is e. g. readily biodegradable for the REACH standard information 9.2.1.2 to 9.2.1.4, 9.2.3 and 9.3.3 the study is not required (EC 2006).

4 Conclusions

4.1 Cut off-criteria for the decision on the necessity of a hydrolysis study

Profound information on the REACH information requirement 'Hydrolysis as a function of pH' is available in great amount. Often it is therefore possible to meet the corresponding information requirements of the REACH regulation in a reliable way without performing a hydrolysis study.

Most of the cut off-criteria suggested in this work were presented to and discussed with stakeholders of environmental sciences and regulation (Scholten 2010). In a rough estimation a coverage of >80% was determined. Hence, for more than 80 % of the REACH substances a hydrolysis study is – according to the cut of-criteria suggested in this work – unnecessary and could be avoided. Given a total number of pre-registered substances of above 130,000 (Daginnus 2009, Öberg and Iqbal 2012) this is a significant total number of hydrolysis studies which could be avoided. Resulting benefits would be significant emission reduction and savings of raw materials, energy, time, laboratory capacity and thus cost.

4.2 Comparison of parent compound and hydrolysis products with respect to physical chemical -, environmental fate - and ecotoxicology data

Comparison of parent compound and hydrolysis products with respect to selected parameters revealed that general trends exist for molar mass and octanol-water partition coefficient (both being generally/mostly lower for the hydrolysis products) and water solubility, half-life for hydrolysis and acute effect concentrations (all being generally/mostly higher for the hydrolysis products). These trends and the specific exceptions are highly relevant when unnecessary negative effects on humans and/or the environment are to be avoided during the development of new chemicals already (see also chapter 4.3). These trends are also worth to be considered when the characteristics of parent compound and its hydrolysis products are verified in detail to improve the overall efficiency of a

process. By this emission reduction and savings of raw materials, energy and plant equipment and thus cost are possible.

4.3 Opportunities for product innovation

Two major objectives were found in the scientific literature: i) abiotic hydrolysis stability of the active chemical substance is adjusted (enhanced or reduced), ii) its release is to be controlled in space and/or time.

When chemicals with enhanced hydrolysis stability are developed the resulting benefits are additional applications and/or improved service life.

Another and more general aspect of adjusting the hydrolysis stability of a chemical substance is to have the stability required and the half-life in the environment well-balanced. Avoidance of unnecessary persistence - and other unnecessary negative effects on humans and/or the environment - should thus become an important factor during chemical product design and development already. This would be a clear step forward towards inherently safe chemicals. Resulting benefits are: qualitative emission reduction, less strict classification and labeling and by this lower water endangerment class, reduced number of studies and dossier work per substance registration, lower on site technical safety requirements and thus significant cost savings.

Controlled release or delivery of the active chemical substance from a hydrolysable precursor, matrix or capsule is used to obtain higher substance concentrations at the target location or to maintain effective substance concentrations for a longer time with just one dosing. In both cases improved efficiency results since a lower amount of substance is needed to achieve a certain effect. The resulting benefits are: quantitative emission reduction due to reduced substance release into man and/or environment, savings of raw materials, consumables, chemicals and energy and the resulting cost savings.

4.4 Key messages

i) Profound information on the abiotic hydrolysis characteristics of organic chemical substances is available in great amount.

ii) It is recommended to make use of this information
- to avoid unnecessary hydrolysis studies,
- when the chemistry of the parent compound and its hydrolysis products has to be investigated in detail for process improvements,
- when the hydrolysis stability of a chemical is to be enhanced,
- to avoid unnecessary negative effects of new chemical substances already during the design and development phases,
- when the efficiency of chemical substances has to be improved by controlled release - and delivery systems.

iii) The resulting benefits are:
- emission reduction (quantitative and/or qualitative),
- savings of raw materials, consumables, chemicals, energy, technical laboratory - and/or plant equipment, time and laboratory capacity,
- cost savings.

5 Abstract

Abiotic hydrolysis can be defined as non-enzymatic cleavage reaction of an organic chemical substance with water and is an important environmental fate process. According to the REACH regulation information on the abiotic hydrolysis behavior has to be available for all substances manufactured or imported in quantities of 10 tonnes or more per year per manufacturer or importer.

The goals of this work were:
i) to prepare unequivocal cut off-criteria for the decision if a hydrolysis study has to be performed to fulfill the information requirements of the REACH regulation;
ii) to compare the chemical structures of parent compound and hydrolysis products with respect to their impact on selected physical chemical -, environmental fate - and ecotoxicology data;
iii) to discuss opportunities for exploiting hydrolysis know how for product innovation.

Unequivocal cut off-criteria for the decision if a hydrolysis study has to be performed were deduced on the basis of the relevant information available in the REACH regulation, the scientific literature and test guidelines. The suggested set of criteria consists of reliable information about annual tonnage, biodegradability, water solubility, classification as inorganic, known hydrolysis (in)stability and volatility. In a rough estimation a coverage of >80% was determined indicating that for the great majority of REACH substances a hydrolysis study is - according to the suggested criteria – not necessary and could thus be avoided.

Comparison of parent compound and hydrolysis products with respect to selected parameters revealed that general trends exist for molar mass and octanol-water partition coefficient (both being generally/mostly lower for the hydrolysis products) and water solubility, half-life for hydrolysis and acute effect concentrations (all being generally/mostly higher for the hydrolysis products). These trends and the specific exceptions are highly relevant when unnecessary negative effects on humans and/or the environment are to be avoided during the

development of new chemicals already. These trends are also worth to be considered when the characteristics of parent compound and its hydrolysis products are verified in detail to improve the overall efficiency of a process.

During the literature search for opportunities for product innovation two major objectives were found: i) the hydrolysis stability of the active chemical substance is to be adjusted (enhanced or reduced), ii) its release is to be controlled in space and/or time.

Expert know how on abiotic hydrolysis can be used to rationally develop new or modified products with - if required - enhanced hydrolysis stability and by this superior technical performance. On the other hand this know how can be used to avoid unnecessary persistence - and of course other unnecessary negative effects on humans and/or the environment – already during chemical product design and development, which is a clear step forward to the rational development of inherently safe chemicals.

Controlled release of the active chemical substance from a hydrolysable precursor, matrix or capsule is used to obtain higher substance concentrations at the target location or to maintain effective substance concentrations for a longer time. In both cases improved efficiency results since a lower amount of substance is needed to achieve a certain effect.

It is recommended to make use of the substantial information on abiotic hydrolysis of organic chemicals available to avoid unnecessary hydrolysis studies, for process improvements, when chemicals with enhanced hydrolysis stability are required, to avoid unnecessary negative effects of new chemicals already during design and development and when the efficiency of chemicals is to be improved by controlled release and - delivery systems.

By this hydrolysis expertise can be used to reduce emissions, consumption of natural resources and cost.

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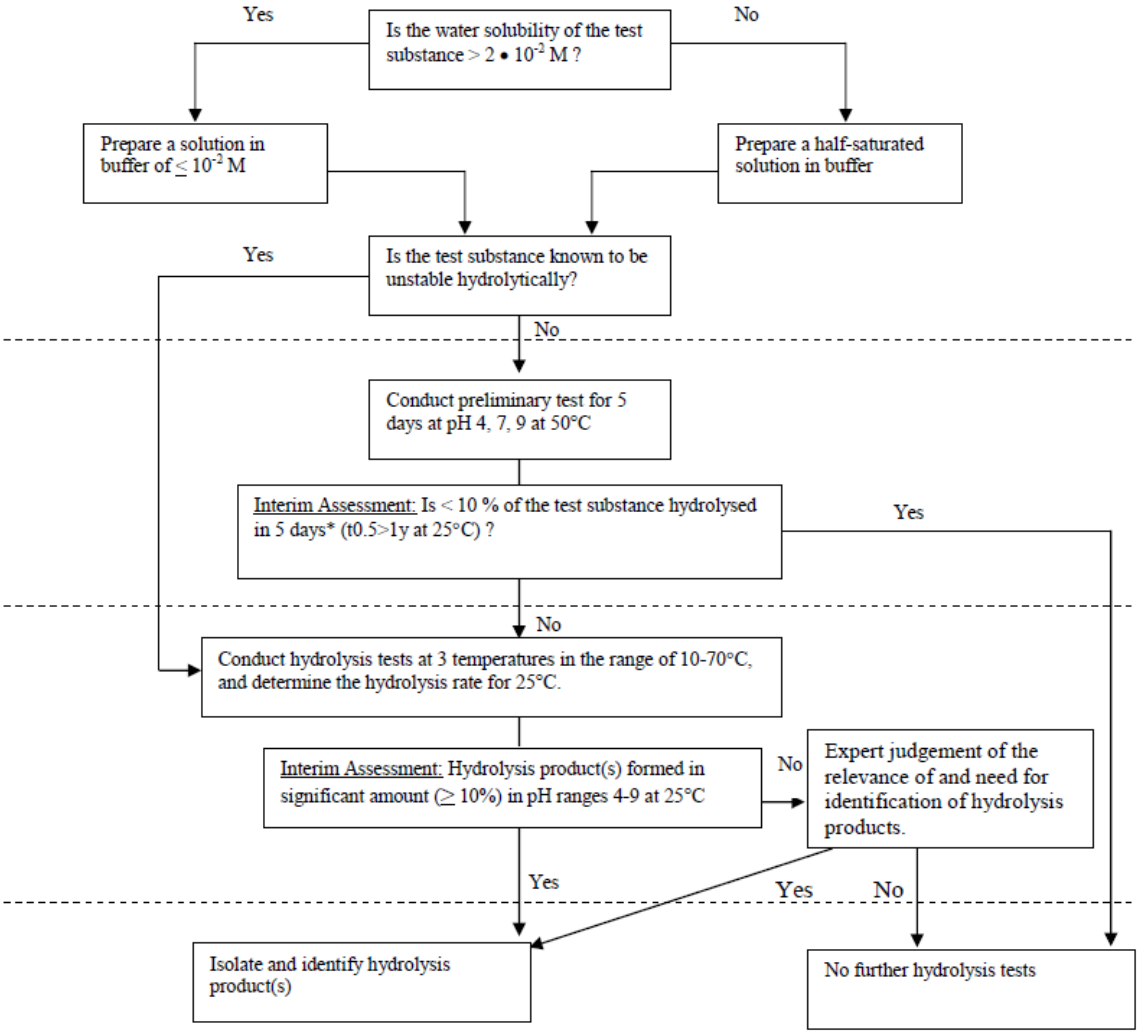
7 Appendices

7.1 Tiered hydrolysis test scheme from OECD 111 (OECD 2004)



* 10 % hydrolysis of a test substance at 50 °C corresponds to a half-life of approx. 30 days which corresponds to a value of approx. 1 year at 25°C.

7.2 Estimation of the half-life $D_{0.5}$ from rate constants (Harris 1990, Kollig et al. 1993)

Hydrolysis described as first order process:

$$-\frac{d[RX]}{dt} = k_{obs}[RX] \quad (1)$$

$$k_{obs} = k_a[H^+] + k_{H2O}[H_2O] + k_b[OH^-] + \sum_i k_{HA}[HA] + \sum_j k_A[A] \quad (2)$$

k_{obs}	*total hydrolysis rate constant [y^{-1}]*
k_a	*specific acid rate constant [M^{-1} y^{-1}]*
k_{H2O}	*neutral rate constant [M^{-1} y^{-1}]*
k_b	*specific base rate constant [M^{-1} y^{-1}]*
k_{HA}	*general acid rate constant [M^{-1} y^{-1}]*
k_A	*general base rate constant [M^{-1} y^{-1}]*
$[H^+]$	*hydrogen ion concentration [M]*
$[H_2O]$	*water concentration [M]*
$[OH^-]$	*hydroxyl ion concentration [M]*
$[HA]$	*general acid concentration [M]*
$[A]$	*general base concentration [M]*

Final terms are dropped, $[H_2O]$ is constant:

$$k_{obs} = k_a[H^+] + \underbrace{k_{H2O}[H_2O]}_{k_n} + k_b[OH^-] + \cancel{\sum_i k_{HA}[HA]} + \cancel{\sum_j k_A[A]} \quad (3)$$

Equation for k_{obs} is written as:

$$k_{obs} = k_a[H^+] + k_n + k_b[OH^-] \quad (4)$$

H^+ and OH^- concentrations are defined by pH:

@ pH=4: $[H^+]=10^{-4}$ M and $[OH^-]=10^{-10}$ M
@ pH=7: $[H^+]=10^{-7}$ M and $[OH^-]= 10^{-7}$ M
@ pH=9: $[H^+]=10^{-9}$ M and $[OH^-]= 10^{-5}$ M

If k_a, k_n, k_b and the pH are given the corresponding k_{obs} can be calculated!

The half-life $D_{0.5}$ is calculated from k_{obs}:

$$D_{0.5} = \ln 2 / k_{obs} \quad (5)$$