# Regulatory (EU) Guidance towards Reduced Chemical Risks: A Study on Unintended Outcomes in Biocide Applications

**Elina Kähkönen**

Aalto University

DOCTORAL DISSERTATIONS

Aalto University publication series
**DOCTORAL DISSERTATIONS** 96/2011

# Regulatory (EU) Guidance towards Reduced Chemical Risks: A Study on Unintended Outcomes in Biocide Applications

**Elina Kähkönen**

Doctoral dissertation for the degree of Doctor of Science in Technology to be presented with due permission of the School of Chemical Technology for public examination and debate in room Stage at the Aalto University Design Factory (Espoo, Finland) on the 4th of November 2011 at noon (at 12 o'clock).

**Aalto University**
**School of Chemical Technology**
**Department of Biotechnology and Chemical Technology**
**Microbiology Research Group**

**Supervisor**
Professor Katrina Nordström

**Instructor**
Professor Ari P.J. Vepsäläinen

**Preliminary examiners**
Docent Tuula Heinonen, Univesity of Tampere, Finland
Ph.D. Jaques Warnon,European Council of producers and importers of paints, printing inks and artists' colours (CEPE), Belgium
Ph.D. Matti Vainio, European Chemicals Agency (ECHA), Finland

**Opponents**
Docent Tuula Heinonen, Univesity of Tampere, Finland
Dosent Arimatti Jutila, Finland

Aalto University publication series
**DOCTORAL DISSERTATIONS** 96/2011



ISBN 978-952-60-4316-6 (pdf)
ISBN 978-952-60-4315-9 (printed)
ISSN-L 1799-4934
ISSN 1799-4942 (pdf)
ISSN 1799-4934 (printed)

Aalto Print
Helsinki 2011

Finland

The dissertation can be read at http://lib.tkk.fi/Diss/

Aalto University

# Abstract

Aalto University, P.O. Box 11000, FI-00076 Aalto www.aalto.fi

**Author**
Elina Kähkönen

**Name of the doctoral dissertation**
Regulatory (EU) Guidance towards Reduced Chemical Risks: A Study on Unintended Outcomes in Biocide Applications

**Publisher** School of Chemical Technology

**Unit** Department of Biotechnology and Chemical Technology

**Series** Aalto University publication series DOCTORAL DISSERTATIONS 96/2011

**Field of research** Microbiology, Chemical (EU) regulations

**Manuscript submitted** 17 May 2011 **Manuscript revised** 20 September 2011

**Date of the defence** 4 November 2011 **Language** English

☐ **Monograph** ☒ **Article dissertation (summary + original articles)**

**Abstract**

This study examines the interactions between the European Union (EU) regulation of chemical substances and product development in the chemical industry. The EU regulatory initiatives that are examined include e.g. REACH, 1998/8/EC, 2004/42/EC and selected voluntary guidance. Specific emphasis of the present thesis is placed on biocide applications with reference to unwanted end-results of the guidance, which aims at reduction of chemical risks. Here, the end result of chemical risk reduction is determined by the interactions between the physico-chemical environment of the application and the prevailing microbial flora. In order to interpret these interactions the research was carried out by addressing the following research questions: First, what are the drivers of the development of new biocide active ingredients, and, which factors hinder such development? Second, which factors of the currently implemented chemicals regulations (e.g. REACH) and directives (e.g. 2004/42/EC, 2000/60/EC), which aim at reduction of environmental and health risks, can increase the microbiological risks associated with products, which may also result in environmental and / or health risks? Third, which factors could drive towards a situation in which the reduction of a specific chemical risk can result in increased use of biocides and therefore lead to increased chemical risk? The present study shows that the currently implemented EU and directives can lead to increases in both microbial and chemical risks. Increases in microbial risks can be expected as the attempt to avoid persistent materials leads to favoring the biodegradable alternatives and the reduction of VOC emissions favors the water based and even VOC-free products and raw-materials. Furthermore, the acknowledged reduction in the available biocide selection due to directive 98/8/EC implementation and lack of new biocide development due to cost associated to in vivo test requirements together with increasingly susceptible products and processes will increase the likelihood of risk of development of resistant microbial species and, i.e. leading to increased microbial risk. The increase in chemical risks due to increased use of biocides is also possible, if the production – scale levels of biocides and the occupational and health risks associated with such amounts are not carefully evaluated. It is therefore proposed that in order to avoid unwanted end-results it is important to improve education for chemical industry product development and purchasing personnel on the evaluation of chemical risks and control of such risks. Moreover, the proactive anticipation of microbial risks during the introduction of new technologies should be assessed. Finally, the development and introduction into usage of alternative means for in vivo tests must be further enforced.

**Keywords** biocides, REACH, directive 98/8EC, chemical product development

**ISBN (printed)** 978-952-60-4315-9 **ISBN (pdf)** 978-952-60-4316-6

**ISSN-L** 1799-4934 **ISSN (printed)** 1799-4934 **ISSN (pdf)** 1799-4942

**Location of publisher** Espoo **Location of printing** Helsinki **Year** 2011

**Pages** 158 **The dissertation can be read at** http://lib.tkk.fi/Diss/

Aalto-yliopisto

**Tiivistelmä**

**Aalto-yliopisto, PL 11000, 00076 Aalto** www.aalto.fi

**Tekijä**
Elina Kähkönen

**Väitöskirjan nimi**
Lainsäädännöllinen (EU) ohjaus kemikaaliriskien vähentämiseen: Tutkimus ei-toivotuista lopputulemista biosidisovelluksissa

**Julkaisija** Kemian tekniikan korkeakoulu

**Yksikkö** Biotekniikan ja kemian tekniikan osasto

**Sarja** Aalto University publication series DOCTORAL DISSERTATIONS 96/2011

**Tutkimusala** mikrobiologia, kemikaalilainsäädäntö

**Käsikirjoituksen pvm** 17.05.2011 **Korjatun käsikirjoituksen pvm** 20.09.2011

**Väitöspäivä** 04.11.2011 **Kieli** Englanti

☐ **Monografia** ☒ **Yhdistelmäväitöskirja (yhteenveto-osa + erillisartikkelit)**

**Tiivistelmä**

Tässä työssä tarkastellaan Euroopan Unionin (EU) kemikaalilainsäädännön (mm. REACH, 1998/8/EC, 2004/42/EC) sekä vapaaehtoisten ohjeistusten ja kemian teollisuuden tuotekehityksen välistä suhdetta. Erityisesti on perehdytty biosidisovelluksiin heijastuviin ei toivottuihin lopputulemiin, jotka ovat seurauksia lainsäädännön ja ohjeistusten mukaisista kemikaaliriskien vähentämiseen tähtäävistä toiminnoista. Näissä sovelluksissa lopputulos kemikaaliriskien pienentämiseen tähtäävistä toimista määräytyy biosidisovelluksessa vallitsevien vuorovaikutusten kautta. Näitä ovat biosidien ja fysikaalis-kemiallisen sovellusympäristön sekä mikrobien vuorovaikutukset. Näiden vuorovaikutusten tulkitsemiseksi työn tutkimuskysymykset ovat: Ensiksi, mitkä tekijät ovat uusien biosidien aktiiviaineiden kehityksen ajureita ja mitkä tekijät puolestaan estäjiä? Toiseksi, mitkä tekijät parhaillaan implementoitavissa kemikaaliregulaatioissa (REACH) ja –direktiiveissä (esim. 2004/42/EC, 2000/60/EC,), jotka tähtäävät ympäristö- ja terveysriskien pienentämiseen, voivat lisätä tuotteen mikrobiologista riskiä, josta seurauksena voi olla ympäristö- ja/tai terveyshaittoja? Kolmanneksi, mitkä tekijät voivat johtaa tilanteeseen, jossa tietyn kemiallisen riskin pieneneminen johtaa lisääntyneen biosiden käytön kautta kemiallisen riskin kasvuun? Parhaillaan implementoitavista EU regulaatioista ja direktiiveistä todettiin voivan seurata sekä mikrobiologisen että kemiallisen riskien kasvua. Mikrobiologisten riskien kasvuun vaikuttavat REACHin myötä tapahtuva aineiden biohajoavuuden arviointi ja siihen liittyen pysyviksi todettujen aineiden rajatumpi käytettävyys. Lisäksi VOC-yhdisteiden vähentämiseen tähtäävät direktiivit ja vapaaehtoiset rajoitukset johtavat lisääntyvässä määrin siirtymiseen vesipohjaisiin ja kokonaan VOC-vapaisiin teknologioihin, joihin liittyy kasvanut pilaantumisherkkyys. Havaittu lisääntynyt pilaantumisherkkyys yhdessä todetusti pienenevän biosidivalikoiman kanssa lisäävät riskiä mikrobiresistenssin kehitykselle, joka vuorostaan kasvattaa mikrobiologista riskiä. Kemiallisen riskin kasvu lisääntyneen biosidien käytön myötä on myös mahdollista, jos tuotantomittakaavan biosidimäärät ja niiden aiheuttamat työterveysriskit huomioidaan puutteellisesti. Ei-toivottujen vaikutusten ehkäisemiseksi esitetään siten: kemiallisten riskien arviointiin ja hallintaan liittyvän koulutuksen vahvistamista kemian teollisuuden tuotekehityksen ja oston henkilöstölle, mikrobiologisten riskien proaktiivisen kartoituksen tekemistä teknologiamuunnoksissa sekä uudelleenarviointia biosidien in vivo riskinarviointivaatimusten harmonisoinnista muiden teollisuuskemikaalien vaatimusten kanssa sekä korvaavien menetelmien aktiivista kehittämistä ja käyttöönoton edistämistä.

**Avainsanat** biosidit, REACH, direktiivi 98/8/EC, kemiallinen tuotekehitys

**ISBN (painettu)** 978-952-60-4315-9 **ISBN (pdf)** 978-952-60-4316-6

**ISSN-L** 1799-4934 **ISSN (painettu)** 1799-4934 **ISSN (pdf)** 1799-4942

**Julkaisupaikka** Espoo **Painopaikka** Helsinki **Vuosi** 2011

**Sivumäärä** 158 **Luettavissa verkossa osoitteessa** http://lib.tkk.fi/Diss/

## PREFACE

The present study is carried out in the Microbiology Research Group in Aalto University School of Chemical Technology.

I am deeply grateful to my supervisor professor Katrina Nordström for giving me unique opportunity for research, learning, and teaching in my area of interest. I want to express my warm thanks to my second supervisor Professor Ari Ekroos and his substitute (2009-2001) Erja Werdi for sharing cross disciplinary views of regulatory chemistry. I am also grateful for all my preliminary examiners; Docent Tuula Heinonen, Ph.D Jaques Warnon and Ph.D. Matti Vainio for their valuable advice for finishing my work.

I thank Anu Passinen and Sirpa Möller for the collegial advice during my research and Anna-Maija Hirvi, Irmeli Suikki and Päivi Luomahaara for continual support. I also thank the International Biodeterioration Research Group (IBRG) for sharing their expertise on biocides during my study. I want to express my gratitude for Ecobio Oyj for the opportunity to improve my knowledge.

Finally, I am most grateful for my husband Tero and for my children Hanna and Otto for trust, support and love every day.

But we, in so far as we have power over the world and over one another, we must *learn* to do what the leaf and the whale and the wind do of their own nature. We must learn to keep the balance.

- Ged, The farthest shore by U. LeGuin

## LIST OF PUBLICATIONS

This thesis is based on the following publications (Appendices I-V), which are referred to in the text by Roman numerals

I. Kähkönen E. and Nordström K., 2008. Toward a Nontoxic Poison: Current Trends in (European Union) Biocides Regulation. *Integrated Environmental Assessment and Management* **4** (4), 471–477.

II. Soirinsuo, K., Kähkönen, E. and Nordström, K. (2009). Feasibility of Active Ingredient (AI) Development for New Biocides in the EU. *Journal of Business Chemistry* **6**(3) p. 128-136.

III. Kähkönen, E., Hirvonen, T. and Nordström, K., 2010. New biocide active substances: needs and challenges in the EU as viewed by industry. *Journal of Business Chemistry* **7**(2) p.69-79.

IV. Kähkönen, E., Soirinsuo, K and Nordström, K. 2010.Trends in EU Biocides Regulation, *Chemistry today*. 28 (2) p. 19-22.

V. Kähkönen, E., Passinen, A. and Nordstöm, K. 2011. Does Decreased Chemical Risk Lead to Increased Microbiological Risk? *Toxicology in Vitro.* SSCT 2011 special issue. Submitted 15.9.2011.

**The author's contribution in the appended publications**

I Elina Kähkönen was solely responsible for the collection of the data, the analysis of the data and the presentation of the data. She has also been completely responsible for selecting the focus area of the paper and producing the interpretations of previous and current issues of the field.

II Elina Kähkönen has designed the work together with Kaisa Soirinsuo, as Elina Kähkönen acted also as the instructor of the M.Sc. (Technol.) thesis of Soirinsuo. The collection of the data and the analysis of the data were carried out by the first two authors together with equal input.

III Elina Kähkönen has been responsible for design of the study, the collection of data and execution of all interviews of the study. Elina Kähkönen has been independently responsible for producing the majority of all sections addressed by the publication. Teemu Hirvonen has added selected data on toxicity testing.

IV Elina Kähkönen has been responsible for the design of the paper, the presentation of the data and the interpretation of data in the publication. She has been independently in charge of defining the focus areas of the study and the conclusions as presented in the paper.

V Elina Kähkönen together with Anu Passinen have designed the experimental part of the study. Elina Kähkönen was, however, completely responsible for the analysis of the data and interpretation of the data with respect to regulatory demands and their outcomes. Elina Kähkönen was responsible for producing the manuscript with co-authors.

**LIST OF ABBREVIATIONS**

| | |
|---|---|
| APE | Alkyl Phenyl Ethoxylate |
| AS | Active Substance |
| BMF | BioMagnification Factor |
| BPD | Biocidal Product Directive |
| CFC | Chloro Fluoro Carbon |
| CFP | Carbon FootPrint |
| CLP | Classification and Labelling of Products |
| CMR | Carcinogenic Mutagenic Reprotoxic |
| DSD | Dangerous Substances Directive |
| EFP | Ecological FootPrint |
| EH | Environment and Health |
| EINECS | European INventory of Existing Commercial Substances |
| EMAS | Environmental Management and Auditing Scheme |
| GHG | Green House Gas |
| GHS | Globally Harmonized System |
| H-statement | Hazard-statements |
| LCA | Life Cycle Assessment |
| LD | Lethal Dosage |
| LPS | Lipo Poly Saccaride |
| MIPS | Material Input Per Service Unit |
| MRSA | Meticillin Resistant Staphylococcus Aureus |
| NOAEL | No Observed Adverse Effect Level |
| NOx | Nitrogen Oxides |
| PPPD | Plant Protecting Product Directive |
| OHSAS | Occupational Health and Safety Assessment Series |
| PBT | Persistent, Bioaccumulative and Toxic |
| PG | Propylene Glycol |
| P-statement | Precautionary-statement |
| QAC | Quaternary Ammonium Compound |
| QSAR | Quantitative Structure-Activity Relationship |
| RC | Responsible Care |
| RA | Risk Assessment |
| REACH | Registration, Evaluation, Authorization and restriction of CHemicals |
| R-phease | Risk-phrase |
| RQ | Research Question |
| SDS | Safety Data Sheet |
| Sox | Sulfur Oxides |
| S-phrase | Safety phrase |
| TBT | TriButyl Tinoxide |
| VOC | Volatile Organic Compound |
| vPvB | very Persistent very Bioaccumulative |
| WFP | Water FootPrint |

**List of Directives and Regulations Referred to [Used abbreviation in brackets]**

Directive No 95/2/EC of 20 February 1995 on food additives other than colours and sweeteners.

Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on the market. [BPD]

Directive 1999/45/EC of the European Parliament and of the Council of 31 May 1999 concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labeling of dangerous preparations.

Directive 2002/95/EC of the European Parliament and of the Council of 27 January 2003 on the Restriction of the use of certain Hazardous Substances (RoHS) in electrical and electronic equipment.

Directive 2002/96/EC of the European Parliament and of the Council of 27 January 2003 on waste electrical and electronic equipment (WEEE).

Directive 2003/53/EC of the European Parliament and of the Council of 18 June 2003 amending for the 26th time Council Directive 76/769/EEC relating to restrictions on the marketing and use of certain dangerous substances and preparations (nonylphenol, nonylphenol ethoxylate and cement).
Commission Regulation (EC) No 2032/2003 of 4 November 2003 on the second phase of the 10-year work programme referred to in Article 16(2) of Directive 98/ 8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market, and amending Regulation (EC) No 1896/2000.

Directive 2003/15/EC of the European Parliament and of the Council of 27 February 2003 amending Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products.

Directive 2004/42/EC of the European Parliament and of the Council of 21 April 2004 on the limitation of emissions of volatile organic compounds due to the use of organic solvents in certain paints and varnishes and vehicle refinishing products and amending Directive 1999/13/EC.

Directive 2005/90/EC of the EUROPEAN Parliament and of the Council of 18 January 2006 amending, for the 29th time, Council Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations (substances classified as carcinogenic, mutagenic or toxic to reproduction — c/m/r).

Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. [REACH]

Council Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

Directive 2008/98/EC of the European Parliament and of the Council of 19 November 2008 on waste and repealing certain Directives.

Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labeling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. [CLP]

Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on Environmental Quality Standards In The Field Of Water policy, amending and subsequently repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC of the European Parliament and of the Council.

Council directive of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products 76/768/EEC. OJ L **262** p..169 -200.

Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market. [PPPD]

**CONTENT**

# 1. INTRODUCTION

## 1.1. Development cycles of chemical substances: From phase-in of product to out-phase of risk

The chemical industry[a] has developed and placed on the market an enormous number of substances as product components, additives and as impurities. Chemical substances are used and are part of a wide range of consumer products and perhaps can even be stated to be present in almost all consumer goods, including cosmetics, fuels, surface materials, foods, medicinal products as well as in countless application areas integral to daily life. However, many of these chemical substances have been shown to be responsible for Environmental and Health (EH) risks and hence, their usage has become restricted or completely banned. Famous examples of global bans of chemical substances are Chlorine Fluorine Carbon (CFC) compounds, for causing ozone depletion (UNEP 2009), and Tri-Butyl Tinoxide (TBT) used as antifouling agents in marine applications, for persistent toxicity in the aquatic environment (IMO 2002). Other examples include Alkyl Phenyl Ethoxylate (APE) surfactants, which are banned from detergents in the European Union (EU), as they have been shown to act as endocrine disrupters (EC 2003a). Bans on leaded fuels in the United States (US) and in the EU represent similar cases. Furthermore, defined substances and groups of substances of different emissions are under continuous surveillance and there is a concerted effort for their reduction (EC 2006b). These compounds include atmospheric emissions such as Volatile Organic Compounds (VOC), Nitrogen Oxides (NOx), Sulfur Oxides (SOx) and the more recently recognized Green House Gases (GHG) as well as aquatic Phosphate (P) and Nitrate (N) releases.

[a] The chemical industry is used according to European Chemical Industry Council (CEFIC) definition, excluding the pharmaceutical industry (CEFIC, 2010).

With reference to the above examples, it is clear that the development cycle of a chemical substance or product is not optimal if it leads to a ban or a phasing-out. Moreover, the contradictory properties of such chemicals have become evident only when they have already reached the market and the unwanted properties of the substances have become evident at the point of usage by the consumer or other end user. From an economical and EH point of view it would be much more desirable to be able to detect such EH risks by laboratory testing before even launching the product or the substance. This concern was addressed by the Dangerous Substances Directive (DSD), which was introduced in the EU in 1967 and which aimed at avoiding the market launch of substances with unacceptable EH risks (EEC 1967). The core of the DSD requirements has been chemical Risk Assessment (RA), which included certain toxicity and eco-toxicity tests for all substances above 10 kg annual production before the placement on the market. Based on the tests the substances were assigned chemical Risk-phrases (R-phrases) and appropriate warning symbols. For chemicalsubstances already on the market the authorities defined R-phrases according to available data and continually up-dated information but there was no obligation for testing these substances, which were listed in the European INventory of Existing Commercial Substances (EINECS) before 1981 (EEC 1981). However, this situation has dramatically changed in the EU as of 1991, when first, the Plant Protection Products Directive (PPPD) demanded the review of all the plant protecting products on the market (EEC 1991) and second, in 1998, the Biocidal Product Directive (BPD) enforced these requirements for other biocidal products (EC 1998). Finally, in 2006, REACH implementation widened the existing substance review to cover all the existing substances above 1 ton annual production (EC 2006a). Of these reviews, the PPPD is nearly completed, BPD is still ongoing and REACH has only

started. The quest for all these three initiatives is to define the possible risks related to the use of the substances and products thereof integral to everyday life of the consumer or other industry end-users. Such a goal is widely accepted and justified but the hurdle of implementation is massive and the final outcome is difficult to anticipate. The BPD and PPPD show in small scale what may be expected of REACH, at least with respect to schedule and the substance out-phases. Both BPD and PPPD implementation have resulted in a notable number of substance out-phases. The proportion of the out-phased substances as a result of the BPD exceeds 60 % of those originally listed as the biocide Active Substances (AS), which are used at the EU market (EC 2003b) and for the PPPD 75 % (EC 2009). This reduction of over 600 substances is notable. A major reduction took place during the notification stage as the feasibility of the registration process was pre- evaluated for each AS. Furthermore, in the case of the PPPD, 7 % of AS were not found to be sufficiently safe by the evaluation process to be permitted in the EU market (EC 2009). The full implementation of the PPPD took two decades and currently the BPD process, 12 years after enforcement, is estimated to have completed the review of some 10 % of the substances (EC 2010b, EC 2003b).

Altogether, regulations have taken an increasingly dominant role in directing the complete product development cycle from new substance and product development to the ones already at the market. As an additional perspective, the development of new substances and products thereof as well as further development of the products already at the market by the chemical industry is equally essential for the implementation of regulations. In fact, any regulatory ban or restriction of a specific substance will cause a requirement to reduce or substitute the substance in product(s), which, evidently, call for development of a product without (or with reduced quantity of) the specific substance.

However, the originally intended risk reduction, which stems from the regulatory source, is not necessarily the only product change, which is achieved by the development. Instead, the change of the total sum of the product EH risks may be drive towards unintended outcomes. This is evident as the substituting substances and/or technologies may also bear EH risks associated with the used chemicals or, interestingly, with microbes, which are able to degrade the product. Consequently it is critical to identify 1) the regulatory guidance from the chemical Risk Assessment (RA) to the final guidance tool and 2) the interpretations of the regulatory guidance in the development, which is implemented by the chemical industry. Accordingly, the challenges for the integration of regulatory guidance into chemical industry product development are the focus of the present thesis. More specifically, biocide applications are examined in detail, as these applications highlight the challenges of finding a balance between microbial and chemical risks in chemical industry product development in general.

## 1.2. Biocides development cycles

Biocides[b] are an exceptionally interesting group of chemical substances and products and serve as an excellent example of the challenges of the implementation of regulatory demands at the level of product development. Biocides may be used as exampled to highlight the entire development cycles from placement on the market to recognition of an EH risk and finally to bans or restrictions. The best known example of a biocide and all chemical substances is most probably dichloro-diphenyl-trichloroethane (DDT) plant protecting product, for which, the Nobel Prize was awarded in 1948 but which two decades later became the best known environmental toxin ever recognized (Fisher 1964,

[b] The term biocide comprises substances and products thereof, which are used against unwanted microbes, plants or animals (EC, 1998; EEC, 1991).

Lewis 1985). Similarly, development cycles, which have spanned over decades, include those of phenolic and organo-metal biocides as well as Copper Chromium Arsenic (CCA) wood preservatives (Paulus 2005, Williams 2005). Most recent examples include formaldehyde releasers, which are currently used, and banned only from some eco-labeled products and of which the majority will be out-phased in the future in accordance with implementation of the BPD (RAL 2010a, EC 2003b). Similar to the development cycles of other chemical substances, the controversial properties of biocides have only been recognized when the biocide has already reached the market. Accordingly, the demand for reduced EH risk of such substances calls for replacing chemistries, which may perhaps be referred to as being "safer than" the one on the market. This requirement is a very specific challenge for the biocides, as by definition they must be harmful i.e. biologically active against the target organisms; microbes, plants and animal species, which contaminate processes and products. On the other hand, biocides, which are biologically active agents, should not cause harm to the other non-target organisms (Figure 1). Clearly, such selectivity is difficult to achieve for a biocide as the targets in living cells are the same regardless of whether the cell of organism is harmful or not. In other words, it is challenging to simultaneously achieve the desired activity towards the target cells, which are to be destroyed / deterred, and at the same time prevent any activity towards cells that are not a problem and are therefore non-target cells. Moreover, if an agent is in fact inactive towards the non-target cells, it is important that such an agent still maintains activity against the target cells. (Figure 1).

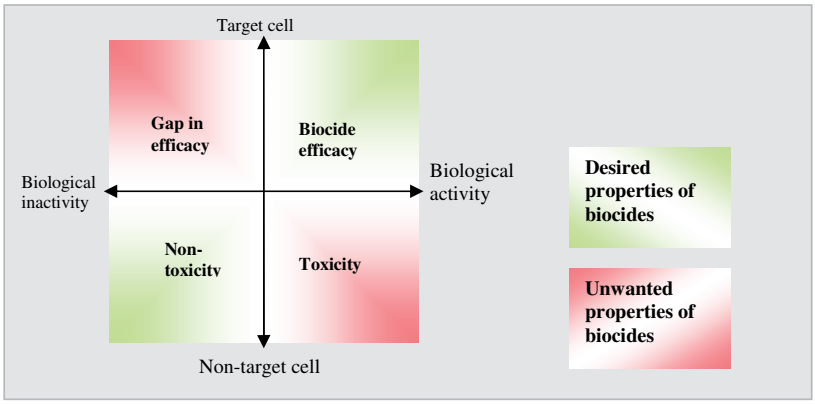


Figure 1 Biocide efficacy (green ) and non-toxicity (green) are desired properties of biocides, whereas toxicity (red) and gaps in efficacy (red) are unwanted. (I)

It therefore follows that increase in biocide efficacy is likely to correlate with increased toxicity, which is, however, unwanted. Then again, biological inactivity of a biocide results in non-toxicity but also correlates with gaps in efficacy and an inability to protect a product from spoilage. This illustrates the dilemma of the product developer who should, according to regulatory demands, avoid harm to non-target cells by formulating a biologically active but non-toxic biocide.

The dual role for biocides as stated by the BPD is outlined as follows *"[…] when properly used for the purpose intended, they are sufficiently effective and have no unacceptable effect […] such as resistance development […] no unacceptable effect on the environment and, […] health*."(EC 1998). Consequently, during development of a new biocide or a product containing biocides, it is critical to define the function of the biocide i.e. the biocide efficacy in the intended product(s) and usage(s). Equally important is the identification of the, EH risks of the biocides, which must comply with safety requirements (EC 1998). An alternative approach to biocide use and development is the development of non-chemical means for preventing spoilage by biological agents, such as heat treatment of wood (Viitaniemi *et al.* 1998), self -polishing or fouling release

coatings (Bruns *et al.* 2005), preventing biofilm formation by electrical instrumentation (Nylund *et al.*1997), or UV treatment of process water (McIlvaine 2005).

### 1.2.1. Biocide usage and function

The purpose of biocides is to preserve 1) a wide range of products ranging from cosmetics and foodstuffs to paints and fuel (EEC 1976, EC 1995, Lindner 2005, Robbins and Levy 2005), 2) materials from wood and masonry to textile and leather (EC 1998, Hauber 2005), and 3) structures including cooling water systems and pulp mills, ships and other marine constructions, where biocides are used as antifouling agents and for prevention of microbial deterioration (EC 1998, Ludensky 2005). In addition, biocides are integral to 4) plant protecting products, which are used against the causative agents of plant diseases in order to prevent crop losses (EEC 1991). Biocides are also used as 5) disinfectants in personal hygiene products and maintaining hygiene in public buildings (eg. swimming pools, disinfection of air conditioning systems) (EC 1998). Moreover, there are also biocides which are used against invertebrates and vertebrates as well as plant protecting products used against weeds but these substances are beyond the scope of the present thesis as the focus is on the biocides used against micro-organisms (EC 1998, EEC 1991).

#### *1.2.1.1. Microbial spoilage*

Microbial contamination of industrial chemical and products and processes is a significant factor in many applications and products. Bacterial species such as

*Alcaligenes*, *Pseudomonas* and *Escherichia* are notable causes of wet stage spoilage of e.g. paints, cosmetics and polymer dispersions (Gillat 2005, Scholtyssek 2005, Lindner 2005). Their action may cause changes in the product properties such as in viscosity, color, pH, odor, and it may appear as gas formation. Visible growth of microbes on wet product surfaces and dry products such as wood, masonry coating or leather is mainly due to fungi and/or algae. The fungal species responsible for deterioration of wood and masonry coating include *Altenaria* spp., *Aspergillus* spp. and *Penicillium* spp. (Williams 2005, Askew 2007) and the algal species include *Chlorella* and *Scenedesmus* (Lindner 2005). In addition to spoilage of products, process fluids and cooling waters also provide a favorable environment for microbial growth. Such growth does, however, not necessarily affect the product quality, but may reduce production process efficiency in fluid flow or heat transfer and may degrade or corrode the process equipment. In these application areas the main focus is on preventing the formation of biofilms by species such as *Pseudomonas*. Biofilms are living multispecies matrixes of bacterial, fungal and algal growth with also other biological agents as part of the matrix. They endure extreme environments as well as biocide activity. Moreover, biofilms provide suitable growth conditions for pathogens such as *Legionella pneumophila*, which may cause lethal pneumonia and may be distributed eg. via contaminated air conditioning systems (Ludensky 2005). Similarly, bacterial contamination of cosmetics by species of *Staphylococcus*, *Clostridium* or *Klebsiella* leads to significant health risks. These may cause allergic skin or eye reactions but also severe sepsis may result if a product, which is contaminated by *Clostridium* spp., is applied to wounded skin (Scholtyssek 2005). In conclusion, unwanted microbial actions lead to economic losses, increases in environmental burden and/or causes notable health risks.

*1.2.1.2. Biocide function*

Biocides must be effective against a wide range of microbial species, as the potential contaminants such as bacteria, fungi and algae are ubiquitous. The contaminating species adapt to a range of different environmental conditions and they can use wide selection of nutrients to proliferate. Algae, for instance, proliferate by simply using $CO_2$ as carbon source and UV light as an energy source. Many bacteria e.g. *Pseudomonas* spp. can use hundreds of different carbon sources from simple to complex compounds. Species with modest nutrient requirements are part of a microbial succession by providing breakdown products, which serve as nutrients for more nutritionally fastidious bacteria and fungi (Askew 2007, Gillat 2005).

Every product or process where biocides are used constitutes a specific microbial growth environment with different conditions such as temperature, water content, substrates, pH, light and oxygen supply, which favor certain species. These species thus become the target group for biocide efficacy and therefore the efficacy of the biocide should also be tested under the specific growth conditions which favor and sustain the growth of the target organisms. Furthermore, these environmental conditions are essential selection criteria when choosing the most appropriate biocide as biocides also function optimally under specific conditions with respect to e.g. pH, temperature and water/solvent content (Paulus 2005). Hence, all the components of the preserved system interact with each other. Namely, there are interactions between the physico-chemical conditions of the product or the process, i.e. of the application and biocides, between biocides and the microbes and between the microbes and physico-chemical conditions (Figure 2).

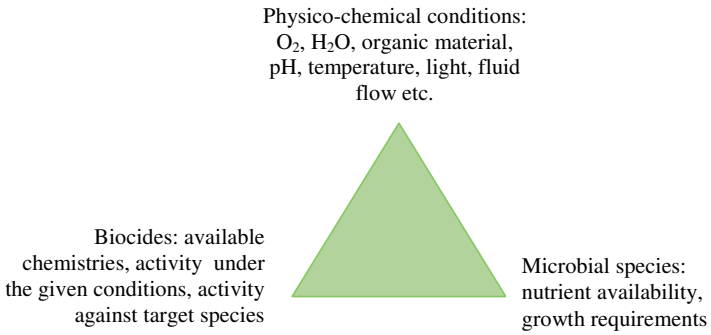


Figure 2. Interaction in the preserved system.

Accordingly, the efficacy of biocide function must be determined as follows: 1) biocide efficacy in the usage application, 2) biocide effect against selected species as a function of biocide concentration and 3) biocide activity mechanisms at the level of cellular structures of target organisms

*1.2.1.3. Biocide efficacy in the applications*

Selecting biocides and defining their concentrations for a specific application is a multidimensional task. The basic approach in efficacy testing is to compare products / materials, which differ only by their biocide composition (CTFA 2001, Askew 2007). Testing of biocide efficacy is carried out by selecting of a representative group of critical contaminants and challenging the biocide with these microbes. The criteria for selection of the microbes that should be used are : 1) the species have been identified as product contaminants i.e. they have been isolated from the contaminated product (Askew 2007, Gillat 2005) or are known to prevail under the production or usage conditions, e.g. human

skin flora in cosmetic product preservation tests (CTFA 2001), 2) the microbial challenge should represent relevant microbial types, which have different tolerance against biocides such as Gram negative bacteria, Gram positive bacteria, fungus (mold, yeast, fungi), algae (CTFA 2001, Askew 2007). The efficacies are compared by following the microbial growth in the products containing different biocides and in a control product without biocides. The microbial challenge testing varies by the selection of the species but also by varying the quantity or cell count of the inoculum, the number of repeated challenges and the frequency of the challenge (CEN, 2006a, CEN 2006b, IBRG, 2000, Askew, 2007). The conditions in which the biocide efficacy is tested should imitate the real life situation as well as is practical, e.g. cosmetics which become repeatedly inoculated during their intended normal usage, may require repeated challenge also in the test setting (CTFA 2001). Such real-life simulations are also used by varying testing parameters such as e.g. fluid flows, aeration, stirring and temperature. For example, algicide testing mimics the light and humid environment, in which the algicides are used (Askew 2007). Altogether, as new products, which require biocide preservation are introduced, new modifications of the efficacy tests need to be defined. In case the usage is markedly different from the previously tested applications, it may be necessary to design new tests and new apparatus for testing (Kähkönen *et al.* 2007).

*1.2.1.4. Biocide efficacy as function of concentration*

Minimum Inhibitory Concentration (MIC) is the minimum concentration of a biocide or biocide AS, which is sufficient to prevent the growth of specific microbial species at a specific microbial density. MIC values may be used as guidance when selecting the biocide against defined species as MIC also indicates the gaps in the efficacy of a biocide,

which therefore may need to be complemented by another biocide. For example, a dry film biocide Carbendazim has MIC of 0.1-5 mg/l against the majority of the target species such as *Pencillum glaucum, Aspergillus niger* and *Trichoderma viride*, but the MIC against one important fungus, *Altarnaria alternata,* is over 1000 mg/l (Paulus 2005). This evidently shows a gap in the Carbendazim efficacy, which needs to be complemented by another biocide, e.g. Diuron / OIT with sufficient efficacy against *A.alternaria* (Lindner 2007).

The biocide concentration needs to be high enough, not only to inhibit microbial growth, but also to prevent the development of microbial resistance. Simultaneously, the concentration needs to be low enough to be safe from the chemical risk point of view (EC 1998). The growing concern of chemical risks has promoted the usage of low biocide concentrations close to the MIC, which may lead to the development of microbial resistance (Maillard 2002).

*1.2.1.5. Biocidal mechanisms*

Biocide mechanisms are an important research area, which, according to Maillard (2002) and Russel (2002), is becoming even more important as the range of application areas is increasing with the increases in available process technologies, whereas the number of available biocides is becoming reduced. Regulatory efforts have resulted in many biocides becoming banned or listed as problematic from the point of view of EH criteria, thus narrowing the selection of biocides. Hence, the correct usage of the available biocides is critical. Mechanisms of biocide action are a result of interaction between the biocide AS and the target organ of the microbe. Biocides in general comprise additional

substances e.g. solvents in addition to one or more AS. The biocide AS mechanisms can be divided into three main groups according to the cellular target: 1) disruption of and interference with the function of the cytoplasmic membrane, 2) interference with the state of the cytoplasm and 3) disruption of the structure and the function of the cell wall. The substances which exert their actions as described for the first group, e.g. alcohols, Quaternary Ammonium Compounds (QAC) and organic acids disturb the transportation, respiration and energy processes of the cell. Furthermore, they may break down the membrane and destroy the cell structure. The second type of activity is typical for substances such as glutaraldehyde, silver salts and QAC, which will attack the cell organs and components such as nucleic acids in the cytoplasm. Finally, substances in the third group e.g. chlorine and aldehydes are able to destroy the lipopolysaccaride cell wall of the Gram negative bacteria. Evidently, one substance may have several cellular targets. (Paulus 2005, Maillard 2002, Russel 2003)

Another focus area in research on biocide – microbe interactions at the cellular level are mechanisms of microbial resistance to biocides. Interest in this area growing partly due to the fact that limiting the selection of the available AS will inevitably lead to the continued use of the same AS chemistries, which, in turn may lead to the development of resistant species (Maillard 2002, Walsh *et al.* 2002). Another reason for the growing interest in biocide resistance is related to emergence of antibiotic resistant microbial species such as methicillin Resistant *Staphylococcus aureus* (MRSA) in hospital acquired infections. There is significant concern for development of cross-resistance in the microbial population, which could arise from simultaneous development of resistance to both biocides and antibiotics (Walsh *et al*. 2002). Resistance to biocides is also recognized as

a serious risk by the BPD (EC 1998). Surprisingly, however, this concern is not yet addressed by the PPPD and its amendments (EEC 1991).

Microbial resistance mechanisms to biocides include changes in outer membrane structure and consequent reduction of permeability (Denyer and Maillard 2002). The chemicals may also be pumped out of the cell by efflux-pumps, (Bloomfield 2002) or they may be treated into less harmful substances enzymatically (Gilbert *et al.* 2002). Also the exo polysaccaride layer, which is a film formed around the cell(s) in biofilms is an efficient resistance mechanism as it hinders the contact of the chemical with the target cell (Schulte *et .al*. 2005, Gilbert *et al*. 2002). All these microbial resistance mechanisms may develop along with mutations in the presence of selective pressure i.e. when a cell population is exposed to a biocide, a certain microbial population with activate resistance mechanisms will tolerate the chemical, and have a greater chance to survive and to proliferate. Furthermore, the genetic material, which codes the resistance, may transfer the resistance not only to the descending generations but also to other species. This is particularly likely, if the resistance coding gene is plasmid-encoded (Bloomfield 2002).

### 1.3. EH risks of chemical substances including biocides

The EH risk of a biocide, or any other chemical substance or product plays a pivotal role in the selection and use of the substance. Assessing the EH risks related to different usages of a substance is therefore, a central part of chemical regulations such as REACH, BPD and PPPD. These regulations also define the Risk Assessment (RA) procedure and the methods applicable for RA. The RA methods aim at defining the risks from exposure to the physico-chemical, human toxicological and eco-toxicological properties of the substance. The present thesis will examine the RA with reference to human toxicity and

eco-toxicity, while the physico -chemical properties such as solubility, color, form, boiling/melting point or flammability are not addressed.

### 1.3.1. Toxicological chemical risk assessment

Toxicological tests on a chemical substance model the different ways of human exposure to the tested substance. First, the routes of exposure comprise of oral, dermal, inhalation and eye contact. Second, the periods and substance quantities of exposure vary from a single to chronic exposure and from Lethal Dosage (LD) to a dosage below the No Observed Adverse Effect Level (NOAEL) (Guidotti and Moses 2007). The end points of evaluation of the different exposures include death, impairment of reproduction, cancer and other cellular mutations or organ malformations, sensitation/allergies, skin and eye defects, clinical signs, adverse effects, haematological, biochemical and urine analysis as well as other detected illnesses (Guidotti and Moses 2007, EC 2008a). The real life exposure modeling in the toxicological test procedure is established by the regulatory requirements. Table 1 gives an overview of the basic toxicological RA, which is mainly based on animal models i.e. *in vivo* testing. In the tests in accordance with REACH and BPD the responses in animals; mainly rats, mice, dogs, and rabbits, which are exposed in a defined way; dose, period and route, are studied. Many of the test results are expressed as Lethal $Dosage_{50}$ ($LD_{50}$), or Maximum Tolerated Dose (MTD), which is the dose required to cause lethal conditions in 50 % of the tested population (EC 2008a ECHA 2009, EC 2003e). Furthermore, other symptoms and defects are visually examined especially in the case of skin and eye exposure but also in chronic exposure studies in which the internal organs of the tested animals are carefully studied after death to detect any defects such as tumors or malformations (EC 2008a).

Table 1. Toxicological tests as stipulated by EU regulations for biocides and for substances within the scope of REACH.. The different routes (oral, dermal, inhalation, eye) and periods of exposure (acute, repeated, chronic) as well as the main models (animals, microbes, tissues) used and the major observations in the evaluation (LD50, defects, illness, sensitization).

| Route of exposure | Main models used[c] | Period of exposure (d) | | |
|---|---|---|---|---|
| | | Acute | Repeated (28 / 90) | Chronic[c] (365-730) |
| | | Observations, results | | |
| Oral | Rat, mouse[b] , dog[a] , cells[c] | $LD_{50}$, MTD, illness | MTD | CMR-evaluation[d] |
| Dermal | Rabbit, tissue | $LD_{50}$,MTD defects | Sensitization | CMR-evaluation |
| Inhalation | Rat, mouse[b] , cells[c] | $LD_{50}$, MTD illness, | MTD | CMR-evaluation |
| Eye | Rabbit, tissue | Defects[f] | | |

[a] non-rodent models are required by the BPD and PPPD but not by REACH in the repeated and chronic toxicity (EC 1998, EEC 1991, EC 2006a). [b] Mice are used in the chronic exposure studies (EC 2008a). [c] In mutagenicity testing cell models are not connected to any specific route of exposure (EC 2008a). [d] CMR evaluation is based on pathological findings such as tumors or malformations in the tested and the reference populations. Furthermore, the problems related to reproduction are screened (EC 2008a). [e] Sensitization is studied as a skin irritation reaction caused by a reduced content used in repeated exposure. [f] Defects are differentiated to lesions, cornea opacity changes, redness and oedema, which are ranked (EC 2008a).

Alternative methods i.e. non-animal methods promotion is an important goal for REACH (EC 2006a). These methods include *in silico* tests, which refer to a combination of different methods to compile all the available information of different chemical substances in order to predict the toxicological properties of the studied substance. These read-across methods such as Quantitative Structure-Activity Relationship (QSAR) integrate the knowledge of the structures of the substance and functional chemical groups

within, with the available information of the toxic properties related to similar structures or the same functional groups (OECD 2007). Another approach are the *in vitro* tests, which utilize microbial, e.g. *Saccaromyces cerevisiae* or *Escherichia coli*, animal or human cells e.g. fibroblasts or blood lymphocytes, or tissues such as the human skin model (commercial products EpiDerm™ and EPISKIN™) (EC 2008a). In the case of dermal and eye exposure, the in *vitro* tests are mandatory before the in *vivo* tests. However, these alternative i.e. non-animal tests do not as yet have an equally established position as do the tests in animals. Consequently, the results obtained by using the alternative tests are evaluated by a case-by-case approach. Negative tests results obtained by the alternative test methods, or positive ones in the case of genotoxicity testing, need to be confirmed by animal tests (EC 2006a).

The impacts of chemical substances on humans are also studied by biomonitoring or molecular epidemiology methods. In these approaches, a biomarker e.g. chemical concentration in blood is used to determine the occurred exposure, which is then compared to the effect in the population (Guidotti and Moses 2007). The other perspective is taken in batch tests, which are used in allergy studies. In these tests voluntary, healthy patients with diagnosed allergic disease are exposed to different kinds of studied chemicals via skin. The skin responses (e.g. redness, itching) to the exposures indicate the sensitization for the tested substance (Andersson *et al.* 2007). Hence, the data is no longer based on the models (in *vivo*, in *vitro,* in *silico*) but on real life cases with real life exposures. However, the reliability of the data obtained by such methods does have other drawbacks. Namely, the data is not based on a preliminarily specified test design, but rather on findings associated to unintended exposures. Hence, the test population in such unintended exposure may be small, which reflects on the reliability of the data. This type of epidemiological data can replace the animal test data only when the

weight of evidence is considered to be significant (EC 2006a). On the other hand, epidemiological data can trigger strong regulatory actions as has been the case with the bans on asbestos (Guidotti and Moses 2007).

### 1.3.2. Eco-toxicity of chemical substances

Eco-toxicity studies predict the behavior of chemical substances in the aquatic and soil environment and assess the potential risks to the eco-system, animals e.g. fish and insects, and finally, to human health. The biodegradation / persistence and accumulation properties and their toxicity to the environment are in a central role of the whole assessment. Substances, which are not degradable and are found bioaccumulative in the tests, need to undergo further evaluations concerning long term effects (ECHA 2008). Here, the degradability is defined according to the time taken for microbial degradation to proceed. In addition, the impacts of environmental conditions such as pH on the substance biodegradation are measured. Bioaccumulation is tested by the partition of the substance between water and octanol (water octanol partition factor; $K_{ow}$) and as the biomagnification in fish (BioMagnification Factor; BMF).

Table 2. The eco-toxicity properties measured (aquatic, terrestrial toxicity, degradation, bioaccumulation) and the models used in the evaluation (fish, algae, invertebrates and mixtures of chemicals) as well as the measurements used ($LC_{50}$, IC, EC, defects, substance degradation, $K_{ow}$, BMF) (EC 2008a).

| Properties tested | Major models | Measurements |
|---|---|---|
| Toxicity | | |
| - Aquatic | Fish, algae, *Daphnia manga* | $LC_{50}$[a], IC[b], EC[c], developmental defects |
| - terrestrial | Bees, plants, earthworms, soil microbes | $LC_{50}$<br>IC, EC |
| Degradation | | |
| - biotic | Sewage sludge or equal microbes | Degradation of substance |
| - abiotic | pH gradient | |
| Bioaccumulation | | |
| - solubility | octanol / water | $P_{ow}$ |
| - sorbtion | soil | |
| - accumulation | Fish | BMF |

[a] $LC_{50}$ = Lethal Concentration, [b] IC = Inhibitory Concentration, [c] EC= Effective Concentration

1.3.3. Established criteria compounds

There are substances and groups of substances that have been demonstrated to act as precursors or causes of unwanted phenomenon in the environment. These are known as criteria compounds and for some of them, the harmful properties associated with them have been recognized more than a century ago. The reaction of $SO_x$ and $NO_x$ emissions, as proponents of acid rain, was suggested by Smith in the mid-19$^{th}$ century (Gorham

1982). Also the role of N and P emissions in aquatic pollution was envisioned by the studies of Weber and Neumann in the early 1900' (Hutchinson 1969). Later, smog composition was defined in the 1950s (Pitts and Stevens 1978) and the mechanism of action of endocrine disruptors such as APE was suggested in the 1990s (Colborn *et al.* 1993). Currently all these criteria compounds among tens of other substances and groups of substances are under continual surveillance, monitoring and tightening restrictions (EEA 2009).

### 1.3.4. Chemical risk communication

Chemical risk communication in the EU currently strives towards the Globally Harmonized System (GHS) and the current Classification and Labeling of Products (CLP) regulation applies for all the substances independent of whether they are regulated by the BPD, PPPD or REACH or any other chemical regulation (EC 2008e). Based on the data in the chemical RA, the hazardous properties of a substance are communicated according to regulatory instructions (EC 1999, ECHA 2009). The tools for communication are Safety Data Sheets (SDS), which are documents attached to the chemical product and delivered to the professional users of the substances (EC 2006a). For the consumers the risk communication is presented in the product label as warning symbols and Precautionary – statement (P-statements) / Safety-phrases (S-phrases) according to regulatory demands (EC 1999, EC 2008e).

The Hazard statements (H-statements) according to CLP and the Risk – phrases (R-phases) according to former EU regulation are a result of the interpretation of the test and test results in the risk classification of chemical substances. For instance, the 46 H-

statements associated with the health risks associated to a substance refer to the results obtained by the 20 toxicological tests defined in the REACH test methods regulation or similar tests, for which the weight of evidence is considered high enough (EC 2008e, EC 2008a). This interpretation of the data from the chemical RA to the regulated risk communication is exemplified by the three assessments, which are included in the basic data requirement for the substances in quantities of > 1 tonne / annum; acute oral toxicity (*in vivo*), sensitization *(in vivo*), and ready biodegradability and bioaccumulation as the principle elements of the eco-toxicity assessment (EC 2006a).

*1.3.4.1. Risk communication example 1: Acute oral toxicity*

The $LD_{50}$ values from the toxicity test are interpreted into acute toxicity categories: cat 1, 2, 3 or 4 with reference to the corresponding hazard statements of being fatal (H 300)/ toxic (H 301) or harmful (H 302) if swallowed (ECHA 2009). Currently both risk communications, i.e. risk assessment according to CLP and according to previous regulation (EEC 1967) are in use (Table 3). The warning symbol for toxic substances is still the "Skull and bones"- sign in both the previous and new regulation, but the symbols for harmful substances are different (Table 3). The precautionary statements (P statements), which parallel the H-statements comprise instructions for safe handling such as P264: Wash … thoroughly after handling, P270: Do not eat, drink or smoke when using this product and for the response to exposure; P301+P310: if swallowed immediately call a poison center or doctor/physician.

Table 3. Chemical RA data (LD50), H-statements and warning labels as Hazard classification according to CLP in comparison to previous (EU) R-phrases and warnings (ECHA 2009, EC 1999).

| Risk phrase | Very toxic if swallowed | | Toxic if swallowed | | Harmful if swallowed | |
|---|---|---|---|---|---|---|
| Warning symb |  | |  | |  | |
| **EU R-phrase** | R 22 | | R 25 | | R 28 | |
| **$LD_{50}$** [mg subst/ kg animal] | 5 | 25 | 50 | 200 | 300 | 2000 |
| **CLP Hazard category** | Cat1 | Cat 2 | Cat 3 | | Cat 4 | |
| Warning symb |  |  |  | |  | |
| Hazard statement | H300: Fatal if swallowed | | H301: Toxic if swallowed | | H302: Harmful if swallowed | |

*1.3.4.2. Risk communication example 2: Dermal sensitization*

In the dermal sensitization test the test animals (rabbits) are exposed to the substance to be tested, within an adjuvant mixture. The exposure is done by intradermal injection or epidermal application and the immunological responses are studied up to 14 days after which the animals are re –exposed to the substance (EC 2008a). The extent and degree of the response is compared to the control animals and if at least 30 % of the test group shows positive response, the substance is classified as Sensitizer Cat 1, H317: Skin sensitizer (ECHA 2009).

*1.3.4.3. Risk communication example 3: Biodegradability and bioaccumulation*

The biodegradability and bioaccumulation tests have a central role in eco-toxicity assessment. In the tests defined as “ready biodegradability” the degradation is determined from Dissolved Organic Carbon (DOC), $CO_2$ formation, oxygen reduction and / or

substance quantity reduction (EC 2008a). The proportion of the substance degraded during 28 d will define if the substance is considered readily biodegradable. In case at least 70 % of the substance is degraded during the period in any of the biodegradability tests, the substance is considered biodegradable and does not need to be classified under any of the categories indicating chronic effects to aquatic environment; Chronic Cat 1-4 and H-statement H410: Very toxic to aquatic life with long lasting effects, H411: Toxic to aquatic life with long lasting effects, H412: Harmful to aquatic life with long lasting effects or H413: May cause long lasting harmful effects to aquatic life. The final classification will comprise the aquatic toxicity evaluation, which is not included in the scope of the present examples (Figure 2) (EC 2008a, ECHA 2008).

In case the Octanol-water partition test gives a result of $K_{ow}$< 4, the substance is not bioaccumulative and does not need to be assigned the H413 H-statement above (Figure 2) (ECHA 2009). In the previous regulation the limit for such a requirement was 3,5 (EC 1999). Furthermore, currently a substance with $K_{ow}$ over 4,5 in accordance with REACH may become classified as very Persistent very Bioaccumulative (vPvB) or Persistent, Bioaccumulative, Toxic (PBT) (ECHA 2008). Chemical substances with these classifications need to be authorized in order to be placed on the market in the EU (EC 2006a). $K_{ow}$ and biodegradability will therefore form the basis for deciding if the substance should be assigned the H413 statement (former R53) and/or PBT/vPvB. (Figure 3).

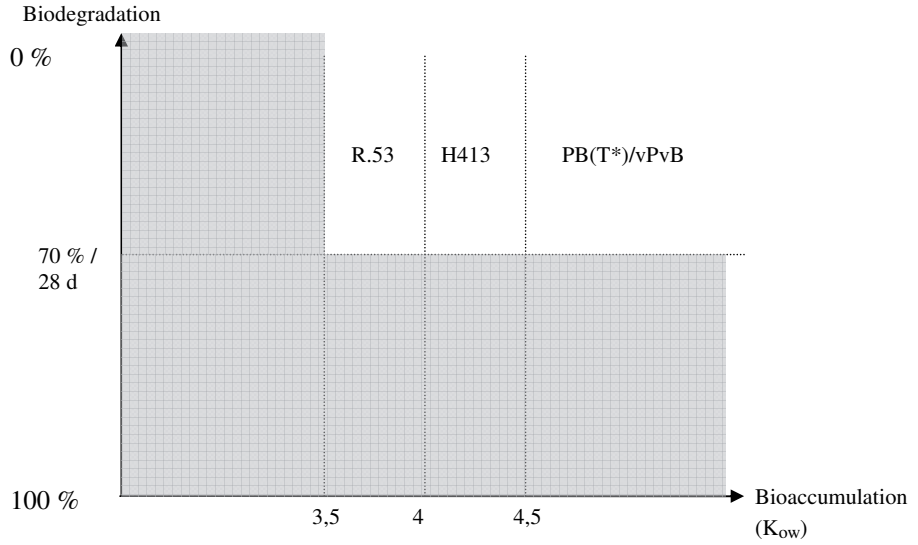


Figure 3. The critical values of the biodegradability and bioaccumulation from an eco-toxicity classification point of view. A degradation by 70 % of the studied substance within 28 d is the limit used in the classifications according to former and also according to CLP. For the bioaccumulation $K_{ow}$ values of 3,5; 4 and 4,5 are limits in the environmental risk classifications (R-phrases, Hazard statements, PBT classification). In the gray area the environmental risks are not considered relevant but in the areas in which biodegradeation is below 70 % and the $K_{ow}$ exceeds 3,5 the classification R 53, H413 or PBT /vPvB are applied. (ECHA 2009, ECHA 2008). * T for toxicity is defined in separate tests.

*1.3.4.4. EH risks of products*

Products may contain many substances, which bear H-statements / R-phrases. Depending on the risk associated with substances and on the concentrations of these substances in the product, the adequate risk classification for the whole product is defined. The risk classification will define the warning label for the end product. The rules for the risk classification of the products are not straightforward and only the basic criteria related to example risk communications above are presented. The generic rule for concentrations triggering a warning label requirement for the product in the cases of acute toxicity categories 1-3 (H 300, H301) is 0.1 w-% and in the case of acute toxicity category 4 (H

302) 1 %. When the substance becomes classified as Sensitizer Cat 1, H317 the trigger concentration is 1 %. However those products, which may become in contact with previously sensitized persons the trigger concentration becomes 0.1 %. Finally in the case of substances, which are classified as with Chronic categories 1-4, the generic trigger concentration for the "dead fish and three" is 25 w-%. (EC 1999, ECHA 2009).

*1.3.4.5. Environmental indicators*

A multitude of environmental indicators are commonly used to visualize the sustainability of a product or service. Sustainability, in turn, refers to sustainable development, which refers to development that meets the needs of the present without compromising the ability of future generations to meet their own needs (UN 1987). Accordingly, this reflects onto the requirements for raw-material consumption and for prevention of pollution, but also to well-being and welfare of society. Hence, the total EH impacts of a product, and the risks associated with all the chemical substances as components are an important element in sustainability. The product Life Cycle Assessment (LCA) of products is an increasingly important approach for communicating the total of the EH impacts from raw-material production to product and finally to waste i.e. including all the EH impacts associated to the different stages of the life cycle (Antikainen 2010). Accordingly, the grand total of the criteria compound emissions is a central factor in LCA (ISO 2006). Evidently, the LCA is not limited only to chemical risks, but includes such factors as land usage and energy depletion, which are inherently tied to sustainability of the products. When the assessment concerns only the criteria compounds related to the climate change i.e. Green House Gas (GHG) the total emission of these gases is communicated as Carbon FootPrint (CFP). The other indicators, which may be

considered to represent alternative routes for risk communication, include Ecological FootPrint (EFP), which focuses on raw-material consumption and land usage during product life cycle. The Water FootPrint (WFP), instead highlights the aquatic pollution and water consumption. The last example, the Material Intensity Per Service unit (MIPS) summarizes all the materials, renewable and non- renewable, consumed in production of a product or a service. All these footprints summarize selected environmental impacts of a product or service throughout their entire life cycle; the water footprint defines the water consumption volumes for the defined product and the ecological footprint gives the indication as surface area of aquatic environment and land, which is required for the raw-material and product production and for the waste treatment with reference to the product unit studied. Another way of expressing the material consumption is used in MIPS, which shows the amount of non-renewable and renewable resources consumed during the product life-cycle (Antikainen and Mattila 2010). Concluding, the above indicators emphasize specific areas of and, hence, inevitably also exclude part of the EH impacts (Figure 4).

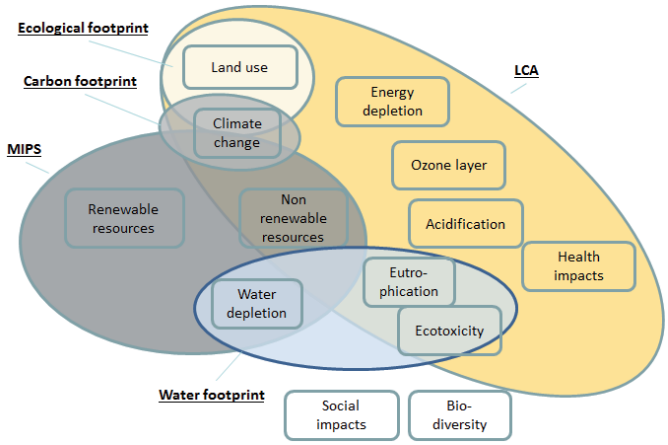


Figure 4. Life cycle impacts on resources (water, renewable, non-renewable, energy), environmental changes (climate change, acidification, euthrophication, ozone layer, eco-toxicity) and health impacts as included in different environmental indicators (CFP, WFP, EFP, MIPS) and LCA (Mattila 2009).

## 1.5. Chemical risk reduction in product development

### 1.5.1. The regulatory framework

Regulatory restrictions may be interpreted as the authorities' reaction to the information obtained on the chemical RA as shown by the examples (Chapters 1.3.4.1 and 1.3.4.2) where the global bans for CFC and TBT are presented. In addition to regulatory demands which actively may ban a substance already on the market, the BPD and PPPD may ban a substance simply by not approving it suitable for the EU market. In the case of PPPD ca. 7 % of the substances have not passed the review process (EC 2009a). On the other hand, the product specific regulations of, e.g. cosmetic and food commonly have lists of substances permitted in the defined usages and the removal from the list is a definitive ban (EEC 1976, EC 1995). The restrictions may also concern a whole group of substances in specific products e.g. ban on CMR substances exclude them from any consumer preparations (EC 2005). Furthermore, the criteria compounds are a common target for restrictions as is the case in the VOC restrictions in paint products and restrictions on VOC emissions from a manufacturing unit (EC 2004, EC 1999). Hence, the regulatory restrictions cover the entire supply chain of chemicals (Figure 5). In addition to the restrictions, the authorities may use financial tools, such as taxes and fees, but these are beyond the scope of the current study. Furthermore, the local procedures for the environmental permissions for production and international agreements concerning the logistics are not examined.

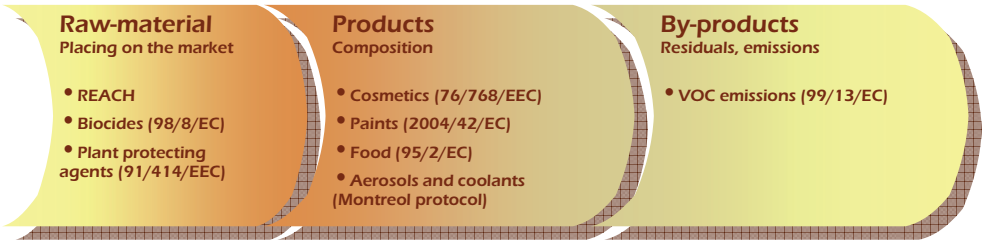


Figure 5. Examples of the regulatory framework along the supply chain from raw-materials and the placing on the market of the substances to product specific restrictions on the composition and to residuals, emissions and other by- products.

However, the official restrictions are not the sole guidance given for and taken by the chemical industry. Firstly, the companies do not necessarily wait until a regulatory restriction is enforced but they may implement the future regulation in advance i.e. to take "early adapter" actions in the development. Secondly, reducing chemical risks has an important role in the product marketing e.g. the marketing phrase "free of a substance " is widely used as are also more multidimensional and specific eco-labels. Thirdly, reducing chemical risk is an important part of company policy which also influences company image and profile amongst stakeholders.

### 1.5.2. Early adapter approach

The chemical industry follows the preparation and revisions of the regulations concerning their own products, raw-material base or the production process requirements. The actual enforcement and implementation of a regulatory instrument may take decades, but the early adapter or first mover will implement the requirements in their own products and processes proactively. The definition of early adapters is well ingrained into the marketing and strategy literature and refers to actors who introduce new innovations to the market (Kerin *et al*. 1992). Currently, the early adoption approach has also become

part of the context of implementation of environmental regulations. The early adapter approach in this context can be argued to stem from economic and ecologic considerations and to be in line with the Porter hypothesis, which proposes that the early adapter may get competitive advantages by the introduction of the new technology (Frohwein and Hansjürgens 2010). Indications of approaching regulations or changes are e.g. authorities' working documents or studies such as recent review on paint directive 2004/42/EC of Tebert *et al.* (2009) or the revisions of the substance lists e.g. candidate list for Substance of Very High Concern (SVHC) in REACH or list of priority substances under review in the Water framework directive (ECHA 2010, EC 2008f).

### 1.5.3. Eco-label criteria

The eco-label organizations set specific criteria for the sustainable composition and EH impacts of a product. By fulfilling the defined criteria, the company may buy a right to use an acknowledged label in their product marketing (RAL 2010, NE 2010, EU 2010). In the criteria defined substances, groups of substances or substances bearing a defined hazardous property may be restricted. This is exemplified by different eco-label criteria and the regulations on interior paint products (Table 4). Eco-labels may well be considered as an incentive to go for early adoption development.

Table 4. Examples of eco-label criteria of chemical composition of interior paint.

| Restrictions on | Blue Angel[a] | EU Eco-label[b] | Regulatory limits |
|---|---|---|---|
| VOC | 700 ppm | 15 g/l | 30 g/l[d] |
| VAH* | | No, traces < 0,1 w-% | <0,1 w-% CMR[e] |
| Heavy metals | No Cd, Pb, Cr(6) | No Cd, Pb, Cr (6), Hg, As, Ba (excl. $BaSO_4$), Se, Sb, traces < 0,01 w-% | <0,1 w-% CMR[e,f] |
| APE** | no | no | Ban in other products than paints (e.g. detergents)[g] |
| Biocides | 13 combinations | | BPD,[h] |
| - CIT/MIT | < 0,0015 w-% | < 0,0015 w-% | Wrng label ≥ 0,0015 w-%[f] |
| - IT*** | < 0,02 w-% | < 0,05 w-% | |
| - FA**** | No, traces < 0,001 w-% | Free FA from formaldehyde releasers < 0,001 w-% | Wrng label ≥ 0,2 w-% |
| Risk classes***** | No 23-28, 33, 39-40, 42, 45, 46, 48, 49, 60-63, 68, | No 23-28, 33, 39-40, 42, 45, 46, 48, 49, 60-63, 68; < 1 w-% 43 [I]; < 2 w-% 50-53, 50-52/53 | 45, 46, 49, 60, 61 < 0,1 % (CMR)[e] |

a (RAL 2008), b (EC 2008b), c (NE 2008), d (EC 2004), e (EC 2005), f (EC 2008c), g (EC 2003a), to be enforced in in-can application h (EC 1998), i (EC 1999)

*Volatile Aromatic Hydrocarbon (VAH), **Alkyl Phenyl Ethoxylates (APE), *** IT: Isothiazolinones, **** FA: Formaldehyde, *****Risk classifications are given as here only as R-phrases.

The development requirement for an eco-labeled product may be triggered by the change in the Eco-label criteria e.g. a change in the VOC restriction, an up-date in the biocide positive list or by a change in the substance's risk classification (H-statement / R-phrase).

### 1.5.4. Company policies

The company policies may refer to global ISO 14000, EU's Environmental Management and Auditing Scheme (EMAS), Responsible Care (RC) or Occupational Health and Safety Assessment Series (OHSAS). The first two are in line with one another as EMAS refers to ISO 14000 and their emphasis is clearly in the environmental impacts of the company or production unit (ISO 2004, EC 2003). On the other hand, OHSAS focuses on the occupational safety in a production unit (OHSAS 2011). This perspective is also a central part of the Fair Trade criteria (FTS 2009). Both the environmental and occupational views are included in RC, which is an international chemical industry initiative (ICCA 2008). It is implemented and followed in cooperation between the national industry associations and companies (RC 2010, ICCA 2008). All these initiatives strive to a definition of company specific tangible indicators for environmental and/or occupational health and safety performance, and a system for auditing and communicating the development of the environmental performance (ISO 2004, EC 2003, ICCA 2008). The impact of these tools on the product development may be seen in the attempt to improve the performance indicator value by reducing the usage of hazardous or harmful substances i.e. substances with defined risk classification or the emissions of

criteria compounds (EC 2003). On the other hand, the performance indicator may refer to sustainable technologies such as eco-labeled product prevalence in the product portfolio or share in sales volumes (EC 2003).

### 1.5.4. Profitability of chemical risk reduction

The reduction of risks of chemical substances and their product development is either obligatory or economically favorable to the industry. To be economically profitable, the revenues from the developed safer substance or product must exceed investments in their development within an acceptable timeframe (III). However, it is evident that the costs associated with placing on the market of a new substance may even become an obstacle for product development of substances such as biocides or products thereof (I). On the other hand, the revenues of the developed safer substance or product are not only due to the sales of the specific new substance or product, but the revenues may include the early adapter benefits and improvement or the environmental performance of the company.

It is evident that chemical substances and products thereof are currently in a dynamic situation with reference to risk assessment, risk communication and risk reduction. First, the present implementation of REACH and BPD will generate a significant amount of new data on chemical risks (EC 2006a, EC 1998). Second, the new and existing data will be communicated according to new CLP regulation (EC 2008e). Furthermore, there are clear development needs and also initiatives to further develop the LCA and environmental indicators to improve the communication of the sustainability and EH

impacts of products (Antikainen 2010). Third, the chemical risks reduction is not a monopoly of authorities, but also consumers demand information on the chemicals, which are used in everyday life, which reflects also to buying decisions. Parallel to this, the companies and industries aim at improvements in their environmental performance (EC 2003, RC 2010). Thus, a learning process is ongoing, where the outcomes depend on how each party eventually interprets the data on chemical risks.

## 2. AIM OF THE STUDY

This thesis strives to identify the potential unintended outcomes of chemical risk reducing regulations and other policy instruments with reference to biocides and biocide applications. Evidently, the need to reduce the risks of chemicals to the environment, the user and the consumer is clearly called for in these applications as well as in other products of the chemical industry. However, due to interactions in biocide applications, the outcome is not easily predictable (Figure 2). An attempt to reduce a chemical risk in these applications leads inevitably to changes in the physico-chemical composition of the application. The changes in the physico-chemical composition, in turn, will influence the ease at which a particular raw material, process of product becomes susceptible to microbial attack i.e. the application may become increasingly biodegradable. This is particularly evident when the chemical composition of the biocide is changed. Consequently the change in the chemical composition of the biocide application may render the final application more susceptible to microbial deterioration, i.e. increase the microbial risk. A change in the susceptibility of the raw material, process of product to microbial deterioration therefore leads to a need to change the biocide. This, again, will change the chemistries present in the application, which means that also the chemical risks are changed. Moreover, even in a static situation with constant chemical (incl. biocides) composition, contaminating microbes may develop increased resistance to the biocide, which is also a manifestation of microbial risk. Concluding, when the regulatory instrument is implemented to reduce the chemical risks of a biocide and the application in

which it is used, the interactions between the chemical composition and microbial species will impact the final outcome.

Accordingly, three potential scenarios concerning attempts to reduce chemical risks in biocides and biocide applications are presented, namely regulatory initiatives which lead to 1) a static situation with fixed biocide composition, 2) increased microbial risks, and 3) increasedchemical risk. The final aim is to 4) propose tools to avoid the unintended outcomes. To address these issues this thesis will set the following Research Questions (RQ), namely:

RQ 1; A static situation. Which are the market drivers and regulatory bottlenecks associated with a possibly stagnated development of biocide Active Substances (AS) currently and in the future? A static situation is clearly not an intended outcome for regulatory instruments, which aim at enhancing the development of chemical substances and products thereof. Furthermore, in the case of biocide applications, the risk of development of resistant species may increase with the usage of a constant AS selection.

RQ2: Increased microbial risk. Which of the currently implemented regulatory drivers of substances other than biocides, guide towards increasingly susceptible raw-materials, products thereof or to increasing risk of the development of resistant microbial species? The number of biocide applications is vast and consequently these applications are influenced by also other regulations on chemical substances and not only by regulations targeting biocides specifically. Evidently, these regulations will also impact on the

chemical composition of the biocide application and hence, may change the product or process susceptibility to microbial degradation.

RQ 3: Increased chemical risk. Which factors may lead to increased chemical risk associated with an elevated need for use of biocides as a consequence of chemical risk reduction and consequent increases in microbial risks? The comparison of different chemical risks associated with alternative product technologies is also addressed.

RQ 4: Guidance toward reduced chemical risks. Which are the tools for avoiding the unintended outcomes? The whole chain from the chemical RA requirements to chemical risk communication and to risk reduction tools, which triggers new development, is examined to highlight the sources for a possibly unintended regulatory driven outcome. Consequent corrective actions are then proposed.

## 3. METHODS AND APPROACH

The focus area of the current thesis is on the guidance tools, which aim at reduced chemical risks associated with biocides and biocide applications and the chemical substances and products thereof in these applications. Moreover, the unintended results of the guidance, such as stagnation of the new substance or product development, increase of microbial risk or chemical risk, and the reasons behind such unwanted end-results are analyzed (Figure 6). The themes are approached in 5 publications (I, II, III, IV and V) in which the research methods are case studies (IV and V), interview (II and III) and profitability analysis (III). All publications stem from setting a regulatory platform (I) with original data on the current regulatory EU framework.

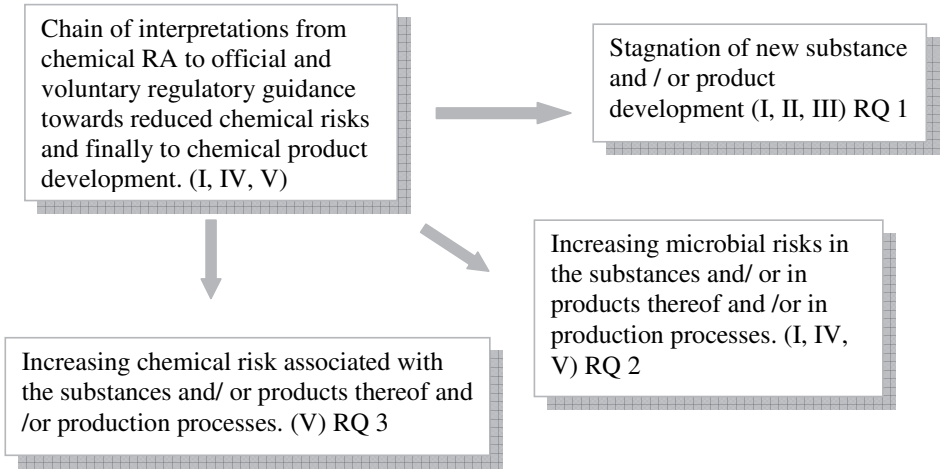


Figure 6. The focus areas of the thesis. The aims of the thesis with reference to each focus area is indicated as the chain of interpretations of chemical risks which are ingrained into each of the three aims and research questions (RQ)

### 3.1. Case studies approach

First, the drivers of biocide development throughout the supply chain (Figure 5) were explored (I). Second, the regulatory guidance towards biodegradability was evaluated (IV) by approaching a supply chain with reference to regulatory guidance, which is interpreted as leading to increased microbial risk. The publication I formed a platform document for the further studies. In both the platform document and the case study, official and voluntary criteria were divided into criteria, which focus on the substances along the supply chain a) as raw-materials to be placed on the market, b) as product components and c) as by-products (Figure 7). The attempt was to elucidate the future challenges related to the control of the microbial risks in chemical products; namely on product properties which drive towards increased susceptibility and, on the other hand, the status of the biocide selection available to meet the future needs. The results for I and IV lead to formulation of the questions in further studies (publication II, III and V).

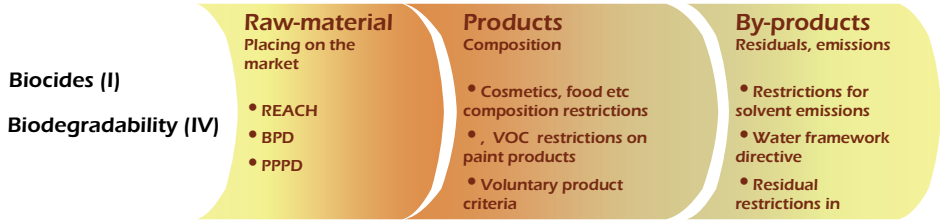


Figure 7. A supply chain perspective on the regulations was used as the basis of interpretations of the platform document (I) and the case studies (IV) (Figure 5, chapter 1.5.) to examine the regulatory influence on biocides development and on the end results of the efforts towards development of increased biodegradability of substances and products.

The third case study (V) combined the results from the previous studies of the biocide development (I, II, III) and on increasing biodegradability (IV). Study (V) focused on comparing the chemical risks associated with product technologies and on avoidance of the development of microbial resistance to biocides. More specifically the focus of the chemical risk comparison was on paint product technologies, which represent an industry, where the implementation of REACH is ongoing, with experiences also from previous regulatory activities such as BPD, and where experience has therefore already been gained. Moreover, the paint industry is a global industry, with very different environmental and demographic challenges depending on the location. Finally, the logistics and supply chains of paint products technologies extend from industrial to developing countries, where the drive towards biodegradability and sustainability is not necessarily under the jurisdiction of EU regulations. The relevance to industry operations with reference to e.g. annual production volume and relevant biocide preservation was verified by a paint industry representative as such data is not publicly available in scientific literature or other sources (V). The instructions for avoidance of the

development of microbial resistance to biocides were composed by benchmarking the WHO guidelines for control of development of antibiotic resistance in clinical use (WHO 2001).

### 3.1.1. Case study methodology

A case may be described as a bounded system, which may either present intrinsic cases; special and notable as such, or instrumental cases, which are used to exemplify selected issues (Stake 1995, Miller and Salkind 2002). Case studies are commonly used in political and legal studies and in examination of contemporary phenomena (Miller and Salkind 2002, Tellis 1997, Yin 1981). In the present thesis the platform document on the EU regulatory framework and biocide development (I) and the resulting implication of increased biodegradability (IV) may be described as instrumental cases as their attempt is to present the current trends concerning the chemical industry at large by using focused case-examples. The platform document (I) may also be defined as an exploratory case study, which refers to data collection prior to further research (Tellis 1997). Study (V) focused on comparing the chemical risks associated with paint product technologies represents an intrinsic case study approach as a case itself can be argued to bear the main message.

### 3.1.2. Case study limitations

The basic question related to the case studies is: How relevant is the result given by the single case in any larger context ? (Yin 1981, Tellis 1997). Accordingly, the case studies focus on the presented RQs by supply chain approach, which is structured to resemble any chemical industry segment (Figure 5). Furthermore, the case study approach is considered justified in the present research of contemporary phenomena (ongoing regulatory implementations) in real life context (chemical industry), in a situation, where the context and phenomena cannot be clearly separated nor can they be experimented on (Yin 1981).

## 3.2. Interviews

### 3.2.1. Interview methodology

Interview methods are commonly divided into structured (questionnaire), half structured (theme interviews) and unstructured (Hirsjärvi *et al.* 2000). Altogether 25 interviews with 31 persons were conducted (II, III). The majority, 16 total were oral theme interviews and the rest, 8 total, responded in writing to the questionnaire, with one exemption (Anon 2008).

The main emphasis was on the oral theme interviews, which were conducted personally. In such a setup, the interviewee has clearly the central role (Hirsjärvi and Hurme 2000)

and the situation enables flexible conversation. This openness, in turn, may even be seen rather as data generation than data collection (Manson 1996). However, despite the openness and flexibility of the theme interview, the interviewer leads the conversation according to his/her agenda. One essential factor for creating the described situation is trust (Chirban 1996) and, hence the confidentiality was emphasized in conducting the interviews and analyzing the data. Accordingly, the data was handled anonymously and before the data was published, the interviewees had the possibility to comment on the text.

All the oral interviews were recorded and transcribed, after which the replies were combined under each question. The majority of the orally presented questions were the same as in the questionnaires, for which written replies were given. The replies for the same question were treated equally with no bias to the oral or written formats. In the case of the oral interviews, some were open theme questions, in which the replies required dealing with a large amount of text. After the transcribing and combining, the replies were double filtered to identify the main points. The topics of the questions are presented in table 5

Table 5. Interview themes and use of data

| Themes | Information gathered | Role of information in the interpretation of data of interview data |
|---|---|---|
| Company information | Size, regional activity, role of biocides in business | Evaluation of the relevancy of replies in terms of experience of the interviewee and the company activity with reference to biocides. |
| Interviewee information | Working experience with biocides | |
| BPD Implementation | Opinions on possibilities of BPD for achieving set targets<br>Evaluation of the impacts of the BPD on biocide offering<br>Comparison of BPD to the other regulations. | Achieving up-to date perspective of the implementation of the BPD<br><br>Evaluation of significance of the out-phasing of AS due to BPD and needs for a new biocide.<br>To obtain industry views on other regulations in order to suggest concrete models for improvements. |
| Need for new AS | Opinions on applications, for which new biocides are needed<br>Specifications for new AS development | Up-to date views from biocide suppliers and users to complement literature available on new biocide AS needs in applications.<br><br>Properties considered important for a new biocide |
| Feasibility of new AS development | Technical perspectives<br><br>Cost estimations | Obtaining current views from the biocide industry on the technical possibilities for developing a new biocide AS<br>Achieving an evaluation of the development cost structure and regulatory requirement thereof |
| Enhancement of new AS development | Views on functioning of regulatory tools, need for research | Achieving industry perspective of the possible ways to activate development |

### 3.2.2. Research population

The interviewees were carefully selected, as the main emphasis was in the quality of the responses and on the expertise of the interviewees instead of the number of respondents. The expertise of the interviewees was considered to be very high, as the majority of interviewees represented members of International Biodeterioration Research Group (IBRG), which is an OECD-based organization dedicated to research on industrial biocide applications (IBRG 2009). The members represent large companies producing biocides, and companies using biocides, as well as members form academia, Non-Governmental Organizations (NGO) and service providing companies specializing in microbial control. The rest of the interviews were conducted amongst the Finnish chemical industry using biocides and in two NGO's based in Finland (II, III).

### 3.2.3. Limitations of the interview study

The limitations of the interview study are related to concept validity, selection of the interviewees, content validity and accuracy in transferring of the information (Hirsjärvi an Hurme 1993). Here, the concept comprises the problem setting and framework for the interview, while the content refers to interview formulation including the questions and themes. Further, the errors in transferring the recorded responses to the written form affect the accuracy. Finally, the selection of the interviewees plays essential role; the number and the background of the persons need to be carefully considered. These factors

and the associated limitations thereof are recognized and discussed in detail in publications II and III.

### 3.3. Profitability analysis

The Net Present Value (NPV) was used for the profitability analysis of a new AS development (Equation 1). Here the attempt was to test the conditions in which the new AS development would become profitable during the economic life time of the AS (*T* in Equation 1). The conditions tested were 1) net cash flow from the new AS sales (c in the Equation 1), which was varied between 5, 10 and 20 % and 2) market shares, which are achieved with the developed AS (*s* in Equation 1), for which values 0.3 and 0.4 % were tested. The sought outcome was the payback time when the summarized yearly NPV equal to the investments in developing the new AS. The value for investment on the new AS development ($I_0$ in Equation I) was based on the literature but it was reassessed and further analyzed in publication II. The other limitations on the present method were recognized and further discussed in the publication III.

Equation 1: NPV (III)

$$\mathrm{NPV} = \mathrm{I}_0 + \sum_{t=1}^{T} \frac{c \cdot s \cdot D_t}{(1+r)^t} \quad (1)$$

$\mathrm{I}_0$ = R&D investment

$T$ = economic life of the AI to be developed

$D_t$ = demand of biocides in Europe in year T

$s$ = market share of the AI to be developed

$c$ = net cash flow as a percentage of annual sales

$r$ = discount rate

# 4. RESULTS AND DISCUSSION

## 4.1. RQ 1: Stagnation of biocide AS development (I, II, III)

The industry claim of regulatory bottlenecks hindering the development of a new biocide AS was evaluated by analysis of the current regulatory framework on biocides (I), evaluation of the profitability of the development of a new biocide (III) and by interviews of biocide producing and using industry representatives (II). Concurrently, also the needs for the properties of a possible new biocide AS were assessed (I, II, III).

New safer biocide chemistries are called for especially for use in exterior coatings, in wood preservation, in antifouling applications and as replacement of FR in in-can preservatives (II, III). However, despite these clear demands, new biocide AS development does not seem to attract industry interests as stated by producers and users of biocides (III). The economic bottleneck is clearly the estimated 2.2-3.5 M€ costs, which are largely result from the regulatory demands of the BPD for compliant RA of new chemical product development. More specifically, the evaluated 2.4 M€ investment in the in *vivo* toxicity tests presents an undeniable obstacle as they comprise in excess of 75 % of the total costs of a new biocide AS development and may be a deterrent to development of new AS. On the other hand, it is evident that new biocide AS are called for and the payback time within 10 years can be shown to offer an achievable market share of 0.4 % when the cash flow is 5 % (II, III). Hence, it may be argued, that the development of safer biocides may become profitable even within the current regulatory

framework. Yet, the economic risks are evidently larger for the development of completely new biocide AS than for development of a biocide based on the current AS selection, for which the requirements in BPD call for investments of 250 000 €, which remains below 10 % of the requirements on the AS (III). The current revision of the BPD does not address this issue, which, however, is a major bottleneck. Rather the revision focuses on facilitating the implementation process by giving the European Chemicals Agency (ECHA) a central role in coordination of the process (EC 2009b). However, the improved fluency of implementation and specifically the communication between the authorities and the industry emerged as important issues from the industry point of view (III). Evidently, the actual impacts of this initiative in improving the fluency of AS registration remain to be seen.

### 4.2. RQ 2: Increased microbial risks (I, III, IV, V)

Increase in microbial risk is a potential consequence of the chemical risk reduction due to 1) changes in the raw material base and product composition and 2) changes in the microbial species i.e. increased microbial resistance.

Changes in the raw material base, other than biocides, will result from REACH implementation and the data requirements related. Here the eco-toxicity tests for all the substances in the REACH scope include biodegradability testing (Table 2), which. may become selective criteria for decision if the substance is further evaluated in accordance

with chemical RA, as higher investments are needed for testing of non-biodegradable substances than for the biodegradable ones (IV). Furthermore, a substance, which is shown to be readily biodegradable i.e. of which the microbes degrade at least 70 % of the substance during the selected biodegradability test, may not become classified as chronic eco-toxic nor PBT or vPvB (Figure 3). This keeps such substances in the raw-material base in compliance with eco-labels and (Table 4), they are not required to bear the unattractive “dead fish and three”- label. (IV) Concluding, the raw-material base is guided towards increasing biodegradability, on one hand, by chemical RA on eco-toxic properties, which are defined in REACH and, on the other hand, by risk communication, which is ingrained into the eco-labels and market driven demand for avoiding the warning labels (IV).

The restrictions on the VOC emissions of paints were studied with reference to the currently implemented chemical regulations and are also analyzed in more detail (IV, V). Here, the guidance towards reduced VOC-emissions from paints has driven the technologies development firstly to water-borne and secondly to low VOC or VOC-free products. Both technology shifts increase susceptibility of paints to microbial contamination. The change from solvent-borne to water-borne technologies creates completely new challenges in terms of controlling microbial contamination and growth in water is the most important environmental factor influencing microbial proliferation. Further reduction of VOC will further increase the susceptibility as VOC include substances which have antimicrobial properties and reducing these will evidently lead to further increase in the risk of microbial contamination and subsequent effects of

microbial growth and deterioration of product quality (IV). The current regulation on VOC emissions of paints (EC 2004) will be reviewed in the future and the proposals presented by Tebert *et al* (2009) may become implemented even though the current proposal has been concluded to be unfeasible. This would mean an extension to cover products, such as hairsprays and detergents. Thus, a similar increase in susceptibility to microbial contamination, which has been seen in the case of paint technologies, may become an issue for serious consideration also in these products (IV, V).

Changes in the prevailing microbial species in the processes of the chemical industry, or more specifically, increases in resistance to antimicrobial agents, leads to increased susceptibility of raw materials, processes and products to microbial risk. The increased microbial risk and deterioration of product quality, is directly associated with the continual usage of a constant set of biocides, for which alternatives are increasingly difficult to find, as the selection of biocides is becoming reduced (I, II, III). Today, based on the industry interview (III), microbial resistance development is not as yet considered as important a reason for the new AS development as is the need for reducing chemical risk. This is also understandable, as there is little evidence to directly link microbial resistance development due continuous exposure to biocides to the development of strains with resistance also to antibiotics and similar microbial agents. On the other hand, there is significant concern expressed in the literature that such resistance may indeed be evolving in the environments in which microbes are exposed to constant pressure of biocides. Moreover, the industry may indeed also have to take a different view on this issue as the current restrictions in the AS selection will become even more pronounced as

also other regulatory demands are evolving in addition to the restrictions imposed by the BPD and PPPD. For instance the Water framework aims at protection of the aquatic environment from emissions from all sources, which may be of agricultural, domestic or industrial origin. Moreover, the priority substance lists published under this directive will function as a guidance for avoiding the listed substances and, thus, to out phase the enlisted substances from the usage. Currently, for example, the available plant protecting products, which were accepted by the PPPD, will become out phased due to being listed as priority hazardous substances (I, IV). Similar impacts may be one result of the revision of BPD as it proposes the possibility to phase out already registered substances in case they are found to be too hazardous (EC 2009b). The potential for the development of microbial resistance to biocides is present and, evidently not wanted. On the other handmany of the tools for controlling antibiotic resistance development in clinical use may well be applied also to biocide applications more or less directly (V). With reference to clinical use of antibiotics, the instructions given to patients, dispensers and prescripts on appropriate use of antibiotics together with the improved clinical and diagnostic methods for targeted medication may also be very useful for the biocide using industry. However, this necessitates the development of new, cost-effective and accurate methods for defining a minimum inhibitory dosing level for biocides to be used in specific applications. Biocides are commonly added at the maximum permitted dose as testing for and determining the minimum adequate level of biocides is currently expensive for product development purposes (Pesonen 2011). On the other hand, sharing the development costs and industry collaboration may be a powerful tool for opening up new avenues for the biocide producing and biocide using industry as has been suggested also

by the WHO for the antibiotics industry. (V). In the case of biocide AS development the cost reduction and the incentives should strive to promote the development of cost efficient test methods for chemical risk assessment as a whole, which is currently a major barrier for new biocide AS development (III, V).

An interesting approach in minimization of both microbial and chemical risks is provided by non-chemical tools used in control of microbial risks. Their development has an advantage over the biocide AS development as they are not subject to chemical RA requirements (I). However, none of the currently available technologies appear to fully replace the currently used biocides (III). For the time being, neither new AS nor the non-chemical tools provide perfect solutions and, evidently, the industry is placing most emphasis on the optimization of the usage of the current biocide selection.

### 4.3. RQ 3: Increased chemical risks

The attempt to reduce chemical risk in product development by avoiding certain defined substances with recognized negative EH impacts may lead to an effort to replace such a substance either partly or completely by another substance in a product formulation. However, even if the replacing substance is water, this may lead to an increase in chemical risk as the water-borne raw-materials and products comprise increased microbial risk, which in turn, must be controlled by a biocide. It may thus be argued that the substitution of a component with less chemical risk, will create an end-result in which the chemical risk is increased, possibly reaching the same levels as before changing the

composition of the product, or resulting in an even higher level of chemical risk. In order to highlight such increases in chemical risks a comparison of paint technologies has been examined in the present thesis, where the critical issue is VOC reduction, which is a major driver for paint technology development today. The EU regulatory restrictions for VOC are supplemented by voluntary VOC-restrictions set by eco-label criteria and retail chain purchasing specifications. These VOC-restrictions are not limited to paints but they also apply to paint raw-material suppliers, for whom even zero – VOC specifications are not uncommon (Kähkönen *et al*. 2007). The regulatory VOC restrictions vary from 30 to 200 g/l, while the voluntary restrictions fall between 700 ppm and 15 g/l (EC 2004, RAL 2006, BQ 2006, EC 2008, NE 2008). The environmental reason behind the regulatory restrictions is the role of VOC in atmospheric pollution and smog formation. Notably, VOC form ground-level ozone in a photo- catalytic reaction with NOx (EC 2004). Ozone, in turn, is known to cause respiratory disease and symptoms, as well as crop reduction (Holland and Pye 2006). Surprisingly perhaps, the VOC definition, which is used in the EU refers solely to the boiling point of 250°C or below instead of the ozone forming capability, which is the US approach for definition of VOC (EC 2004, Carter 2009). Both of these VOC definitions apply to a wide range of substances with different kinds of chemical risks e.g. Methyl iso Propyl Ketone (MIBK), which has harmful properties but also to Propylene Glycol (PG), which, however, has also been classified as Generally Acknowledged as Safe (GRAS) and is used even in baby skin care products (OECD, 2010).

In the studied technology comparison case, PG was assumed to be absent from a paint formulation and therefore biocides are needed to preserve the water-based paint. For the

present theoretical comparison it was assumed that the biocide system could be the commonly used combination of 2-methyl-4-isotiazol-3-one (MIT), Chloro – 2 Methyl- 4-isotiazol-3-one (CIT) and 2-Bromo-2-NitroPropane-1,3-Diol (BNPD) which fulfills eco-label criteria. The first concern that arises from the comparison is that the risk associated with the biocide combination may remain unnoticed due to the very low concentrations of biocides, i.e. 15-100 ppm, in the final product. However, in the annual production volumes these minor quantities will add up to tonnage level of a biocide AS, which poses a notable occupational chemical risk (Passmann, 1995). Such levels present a serious hazard particularly in regions such as in many developing economies, where occupational safety during production has not received due attention as yet. In addition to occupational safety, the regional conditions impacting on the production unit and product usage should also be taken into account when comparing chemical risks of paint technologies.

The possible risks associated with either a PG containing paint or an eco – label compliant but biocide containing paint were compared (Table 6). More specifically, the possible outcomes of such different paint product technologies were examined with reference to generally accepted views from the literature (e.g.Fernandez-Redondo *et al.* 2004, Maier *et al.* 2009, o'Driscoll and Beck 1988, OECD 2010, Carter 2009, Holland and Pye 2006) , namely: 1) the risk to ozone formation increases along with increased NOx emissions, which depend on regional traffic density and combustion sources in the region where the PG emissions are generated, 2) The health impacts of the resulting ozone depend on the density of population in the region and the environmental impacts

depend on the proximity to agricultural production areas. Hence, it is justified to propose that the risks related to PG become elevated in regions with high density of traffic and population. On the other hand, it may be proposed that such an outcome equals the occupational risks related to use of biocides, which depend on the occupational safety standards applied in the production. Evidently, it can be deduced that the developing economies face specific challenges with reference to the final chemical risks associated with either increased VOC emissions or increased concentrations of biocides (V).

Table 6. The comparison between the EH impacts of PG and biocides. The impacts are divided in to mechanisms, EH impacts and the factors influencing the EH impact.

| Compound | Hazard indications | Impact mechanism | EH impact | Factors influencing |
|---|---|---|---|---|
| PG | VOC | Atmospheric pollution, ozone formation in the photocatalytic reaction with NOx | Respiratory diseases, crop reduction[a] | Proximity from the NOx sources (traffic, city centres) Speed of degradation before the reaction |
| Biocides (CIT/MIT and BNBD) | R23/24/25-34-43-50/53 R21/22, R37/38-41, R50 [b] | Occupational exposure to human toxins | Allergy, disability to continue work[c] | Occupational safety practices (e.g. application of OHSAS[d], National regulatory requirements) |

a (Holland and Pye 2006), b (RH 2004), c (Fernandez-Redondo *et al.* 2004, Maier *et al.* 2009, o'Driscoll and Beck,), d (OHSAS 2011).

Understanding the actual risk mechanisms and the factors influencing the risk associated to critical compounds, such as VOC and biocides, is crucial when chemical industry product development aims at a total reduction of chemical risks. This becomes evident as the production conditions as well as the usage conditions influence the total risks associated with a product. As a conclusion of the present comparison, it is evident that it is not possible to define a specific paint composition, which would pose minimum total risks under all local production and usage conditions.

### 4.4. RQ 4: Regulatory guidance tools in chemical product development (**I, III**, **IV, V**)

Chemical product development, which aims at reduction of chemical risk may be presented as an outcome of one part of the chain from chemical RA to risk communication and further to risk reducing guidance, and finally to risk reducing activities in chemical product development (Figure 8). More specifically 1) chemical RA is comprised of defined toxicological and eco-toxicological tests (Table 1, Table 2), and risk classification, which is 2) communicated with the H-statements (R-phrases) (Table 3, Figure 3). Furthermore, criteria compounds are those substances, which have been presented as responsible for an environmental impact. These classifications and criteria compounds are reflected in the 3) risk reducing tools, such as eco-label criteria (Table 4), environmental policies of companies, and official restrictive action. As an outcome of this chain, product development will aim at reducing or totally replacing a substance. Moreover, also the unintended outcomes, which have been presented, stem from this chain.

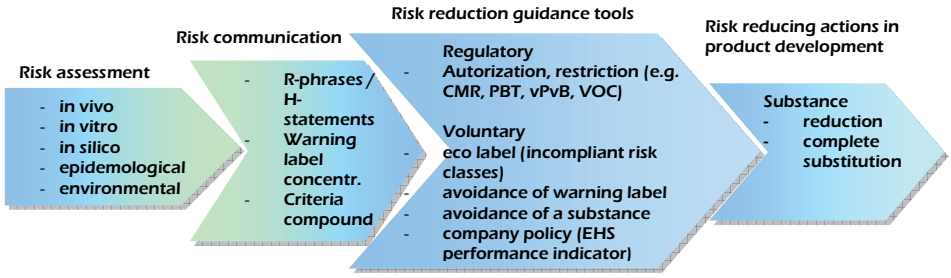


Figure 8. The chain from chemical RA (e.g. *in vivo*, *in vitro*) to risk communication (e.g. H-statements, P-statements) and to risk reduction means (regulatory and voluntary) (ECHA 2008, EC, 2005 EC 2006a, EC, 2010a, EC 2003, I, IV, V).

The required in *vivo* tests in chemical RA have created an economic burden, which has effectively become a bottleneck for the development of biocides with reduced chemical risks and/or with improved efficacy against resistant microbes. Thus, development of new biocidal AS can be enhanced by reducing costs of toxicological methods needed for chemical RA (Table 1). Such efforts may also lead to reduction of in *vivo* tests on vertebrates, which is clearly a desirable outcome (I, II, III). The same outcome is one of the targets of REACH and even more so for the cosmetics directive, which bans vertebrate testing for cosmetic products and raw-materials. Hence, the call for alternative testing *in vitro* and *in silico* tests is evident.

The EU definition for VOC, which refers to a boiling point below 250°C of a substance, is a concrete example of risk communication, which may mislead product development. A replacement of PG by propanoic acid, 2-methyl-, monoester with 2,2,4-trimethyl-1,3-pentanediol would enable to call the product as VOC-free according to the EU definition

despite the fact that both substances have similar properties and risks associated (V). It is evident that such an ambiguous definition may drive the development of substances and products thereof towards compliance with the boiling point requirement rather than towards reduced ozone formation, which should be the aim in the VOC reducing activities. Such “loophole technologies” can only be avoided when those responsible for the development work acknowledge the actual risks associated with the substances including the factors which impact on their total risk. Evidently, however, the regulatory definition of a criteria compound must fulfill many requirements such as being reproducible and practical in addition to correlating with the actual impact of the substance as specifically as is possible.

The regulatory and voluntary guidance towards reduced chemical risks, such as REACH eco-toxicity test requirements together with negative value creation for the non-biodegradable substances (PBT, vPvB authorization, eco-label incompliance, warning label requirement) and VOC reductions on paints, may lead to preferences towards biodegradable and water-borne raw-materials and products (Figure 9). These directions are inherently tied to increasing microbial risks in raw-materials and products thereof as well as in production processes. The microbial risk may be a new factor concerning a product when it comes to changes such as solvent-borne paint to water-borne one. However, also less evident changes, such as further decrease of VOC in water based paint and/or change of a raw-material to more biodegradable one, may lead to unexpected microbial spoilage of the raw-materials, products and processes. The consequent waste creation, cleaning requirements and exposure to contaminated materials in the production

and in the end usage, may create increased EH impacts. Evidently, thiscontradicts the aim for chemical risk reduction, which specifically aims at reducing EH. . Hence, it may be argued that the magnitude and the likelihood of microbial risks should be included as one factor when evaluating the outcomes of a regulation or voluntary instrument, which promotes a shift towards water-borne and/or biodegradable raw-materials and products thereof.

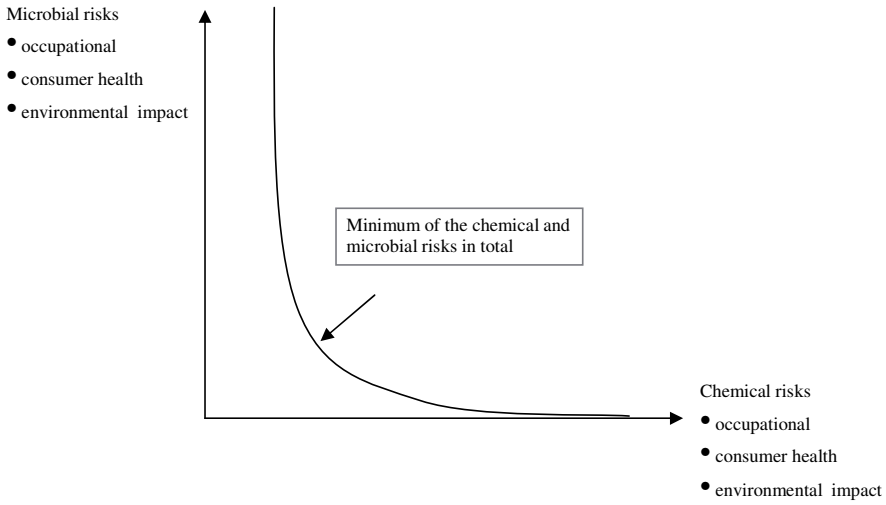


Figure 9. Microbial and chemical risks with reference to biocides usage. The reduction of the chemical occupational, consumer health or environmental risks may lead to increase of microbial risks in products and processes where biocides are used (I).

A straightforward guidance to reduce risk associated to one specific substance may lead to a situation in which another risk associated with the replacing substance increases. The comparisons of the environment and health risk associated with different substances and products thereof are not straightforward to make and many factors affect the certainty of

the result. These factors, which were pointed out in the paint comparisons (V) may be summarized to be related 1) to the definition of the exactness in inventory of the inputs in the production and in raw-material production processes and the outputs of the production and usage and 2) to the basic data on the environmental and health impacts related to product composition and substance inputs and outputs (Figure 11). The composition of the product, which is to be evaluated for chemical risks, can certainly be defined as accurately as is necessary. However, the minor components, such as the biocides, may be unintentionally excluded due to their low concentrations at this stage. Moreover, as the production and usage stage is reached, the major inputs and outputs can be defined, whist the minor components may again, become excluded. Furthermore, at these stages some of the inputs and outputs, such as energy, water, criteria compound emissions etc. are used and created by also other activities of a manufacturing facility, which is typically operating several product lines. Hence approximations are commonly used in inventory of the inputs and outputs. Even more approximations may be necessary when the inputs and outputs from the raw-material (and their raw-material) production are included. Moreover, the EH impacts of the outputs, such as emissions, vary according to the regional population and other emissions (V). In addition, the EH impacts of the substances, also comprise uncertainties (Figure 10). Much of the EH data is still not available and the available RA data is mainly based on different models, which approximate the impacts on humans and in the environment. Accordingly, it is evident that the complete life cycles of the substances and products thereof must be assessed in order to achieve the intended improvements in product technology and to avoid the unintended increase in chemical risks (V). Accordingly, the choice for the best

sustainable product composition should take into account the conditions in the production and usage of the product and its raw-materials.

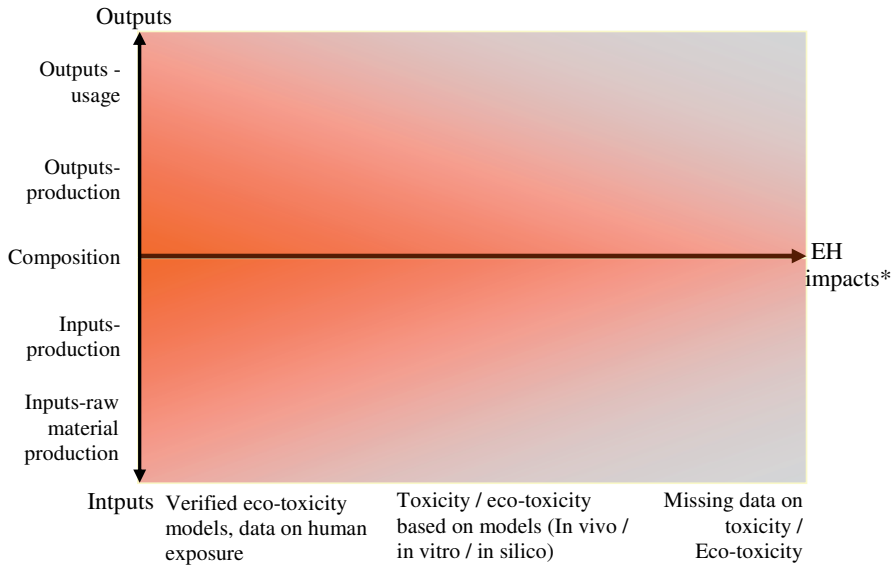


Figure 10. Certainty (orange color) and uncertainty (gray color) in the product comparison with respect to environmental and health impacts. The uncertainty increases in inventory of inputs and outputs when receding from the product composition and when using data from models instead of findings based on actual exposure. *EH = Environment and Health (V).

## 5. CONCLUSIONS

Chemical risk reduction is an essential demand when moving towards more sustainable products and production processes in many industries from electric and electronics (EC 2002a), to agriculture (EC 2000, EEC 1991). Evidently, in the chemical industry the chemical risk reduction is a dominating factor in any development towards improved sustainability. Many of the actual changes towards sustainable products take place in the product development, where the criteria from the different guidance such as regulatory restrictions, eco-label or company environmental performance indicators, is transferred into the specifications for the developed product. However, as elucidated by the present study, there is no universal product composition, which would result in minimum total risks under all the production and usage conditions. Consequently, the product developer is a key person who should be able to compare the EH risks associated to alternative product compositions for the intended production and usage conditions. On the other hand, when the raw material sources (suppliers, production units) are to be selected, the key persons are evidently the purchasers. In general, the current guidance towards improved sustainability in different industries focuses more attention on environmental impacts, while occupational risks tend to have a minor role in public discussion (Hassim 2010) even through the occupational safety perspectives are considered in REACH and socially responsible public procurement has recent guidance (EC 2006a, EC 2010 ). The choice between the occupational risks and the environmental risks was examined in the present thesis by comparing the environmental risk associated to PG and occupational risks of biocides. Evidently, the biocides are not the only causes of occupational risks, but

due their minor content in many applications, they may be easily excluded from critical evaluations and analyses. Interestingly, this comparison is similar to the current discussion on the technology shift from incandescent light bulbs to fluorescent lamps in accordance to compliance with the EU eco-product design directive. The specific challenge with reference to these products is the evaluation of the occupational risks of handling mercury by workers in China in the production of the new lighting technologies vs. the push towards resulting energy savings in the EU (Hashash 2009). Consequently, when aiming at improved sustainability, the developers, those responsible for the scale up to production and those responsible for purchasing of the raw-materials should be fully aware of the basic risks related to chemicals and the factors, which may influence these risks. The product safety data needs to be scaled up to production safety data and the raw-material production conditions must be included in raw-material safety data in order to achieve total improvement in sustainability. Recently, it has also been documented that the education of chemists is inadequate with reference to issues related to sustainability (Hall and Howe 2010). Hence, the first conclusion of the current thesis is that the education of those responsible for chemical product development and production scale up as well as for purchasing should comprise the basics of chemical risk assessment, risk communication and risk reducing tools. Ideally, education on the regulatory aspects of chemical risks should be included in the chemistry programs of higher education institutions within the EU.

Microbial risks will be an increasingly important concern in the chemical industry due to regulations, which aim at reducing chemical risks. On one hand, the shift toward water

based technologies and biodegradable raw-materials will increase the susceptibility of the product to microbial contamination. On the other hand, continuous selection pressure by antimicrobial agents, such as biocides, may result in the development of microbial resistance. In the first case the shift towards increasingly susceptible raw-materials due to biodegradable raw-material base must be accepted as the substance degradation is essential in avoidance of the EH risks associated to persistent chemicals accumulation in the nutrition chain. This guidance concerns all chemical products and not only the biocide applications, which are the focus of the present thesis. In fact, this trend will introduce new products and processes as biocide applications due to increasing use of biodegradable raw-materials. However, biodegradation before the end of the product life cycle is spoilage, which also causes EH risks. Consequently, the second conclusion of the present thesis is that the control of biodegradation should not aim at the prevention of the biodegradation. Rather, the focus should be on the correct timing of the biodegradation; in other words biodegradation should happen as soon as possible after the service life – but not before this. This approach may be seen as a change in the current mindset and it places an emphasis on the chemical producers' responsibility for the control of the end of the life cycle of the product. Similar extension of the producers' responsibility to cover the end of the product life cycle is widely seen in industry e.g. in the requirements specifically for electronic and electric equipment waste treatment and in general for minimization of waste creation (EC 2002b, EC 2008d). In the future, these requirements on the producers' responsibility for the end of the life cycle will also extend to new areas in the chemical industry, e.g. polymers were exempted from REACH, but only until the applicable scientific criteria are established (EC 2006a). In practice, the

integration of the control of biodegradability extends to the product development and scale up to production from 1) raw-material choices and storage conditions to 2) biocide preservation design and efficacy testing in the product, and 3) to production hygiene control procedures. These practices are currently used in the chemical industry but, according to the current thesis, the importance of such actions will increase and they will need to be carefully addressed with reference to new product lines and processes (IV).

Increased microbial risk may also arise via the development of resistant microbes due to reduced selection of the biocide AS. This situation represents clearly an unintended outcome of the chemical risk reduction. The biocide industry and the regulatory bodies should strive to prevent similar trends in possible biocide resistant organisms as has been seen with the emergence of increased and multiple antibiotic resistance. In response to such trends, The WHO (2001) has proposed the decreased usage of antibiotics, which is also of relevance to the use of biocides in applications where overkill doses are used. Such excessive dosing is common practice due to lack of effective methods for determining an adequate level of biocide efficacy in final products (Pesonen 2011). Evidently, this calls for development of such efficacy test methods. Furthermore, rotation of antibiotics in clinical use has been used to reduce the emergence of microbial resistance (Monroe and Polk 2000) and could also be applicable for biocides usage. Currently however, the narrowing offering of AS poses a limit to rotation of the active agents and further highlights the need for new AS development too. It is evident that the interest in new AS development depends on the cost of development, where a key issue is the possible reduction of the costs of *vivo* tests, which are required for the placing on the

market of the biocide AS in the EU. Furthermore, the cost is only one of the motivations in the development of the alternative in *vitro* and in *silico* test methods, as ethical issues have already banned *in vivo* testing in the cosmetics industry (EC 2003d). Moreover, Hartung and Rowida (2009) extend the list of handicaps of the current in *vivo* tests to their evident lack of reliability. In addition to replacement of in *vivo* tests, the reduction of the number of required tests needs should also be considered. Harmonization of the test requirements of the biocide AS with the strictest REACH requirements (>1000 tn/a) would save costs equivalent to some 0,5 M€ only by omitting the testing in dogs (Anon 2008). The reduced testing regime, which approves rodent as models, is still considered sufficient for the highest tonnages in accordance with REACH. The adequacy of the rodent models together with the acknowledged and studied cellular toxicity of the biocides should be re-evaluated. Consequently, these questions must be brought to the attention of the authorities, who are in charge of approving the alternative test methods as standards and evaluating the weight of evidence of the data, which is achieved by the non-standard methods such as epidemiological methods (EC 2006a). Furthermore, while the usage of the alternative test methods is cheap, their development is expensive and thus, the development of such testing would greatly benefit from public funding of research by non-profit institutions such as universities and other independent establishments. (Hartung and Rowida 2010). Summarizing, the third conclusion is that the reduction of both microbial risks and chemical risks associated to biocide applications calls for substantial investment on the development of the cost efficient, alternative methods for vertebrate tests.

Ultimately, however, the principal issue of chemical risk reduction is the profitability of new product development. This also includes the choices made by consumers, as consumer and end-user choice ultimately determines the value of chemical risk reduction. Furthermore, consumer preferences will guide the risk communication as eco-label products and the perceptions of "free-of –a-substance"- products specifically target the prevailing environmental awareness and personal preferences of the greater public. In products marketed as "free-of-a substance" is evident that possible risks related to the products may not be evident to the consumers. It may be questioned, if the development and introduction of these products is ethical in the first place, as the end result may be as ambiguous as the dilemma of choices presented in this thesis (V). Individuals responsible for development and marketing should be introduced to this issue in order to arrive at responsible ethical choices between the EH impacts of the product offering. Furthermore, the authorities in charge of marketing regulations could and should voice a stronger opinion on the misleading nature of the "free-of-a-substance"-statements in product marketing. Finally, responsible communication by the chemical industry is called for in order to improve informed risk communication on which consumer choice is made. This would help the consumer to distinguish attitudes and fears from facts and knowledge (Nystén 2008).

In conclusion, development of sustainable chemical products with reduced chemical risk can be achieved via improved definition of the relevant EH impacts of chemicals. Moreover, such understanding must be scientifically sound and communicated by developers and authorities alike to the consumers and end users in order to support

sustainable choices. Such choices will ultimately decide the interests of the industry to choose the most appropriate technologies and to invest into development of new alternative chemicals and methods for implementation of biodegradable, high quality and safe products and production technologies.

**REFERENCES**

Anon. 2008. Core Data Requirements as per Technical Guidance Document ofn Data Requirements in Support of the EC Directive 98/8/EC Annex IIA-Active Ingredient-Toxicology testing. Charles River. Price estimates as a reply for an interview question. Unpublished data. 5 p.

Anderson, B. E., Tan, C. T. and Marks, J. G. Jr. 2007. Patch-Test to formaldehydes, bioban and other formaldehyde releasers, *Dermatitis*, **18** pp. 92-95.

Askew, P. 2007. *Biocide Basics: An introduction to the Microbiology, Preservation and testing of the surface coatings*, Vincentz Network, Hamburg, Germany. 35 p.

Antikainen R (Ed.) 2010. *Elinkaarimetodiikkojen nykytila, hyvät käytännöt ja kehitystarpeet* (in Finnish). Suomen ympäristökeskuksen raportteja 7/2010, 83 s, Suomen ympäristökeskus (SYKE). ISBN: 978-952-11-3734-1 (PDF). Available at: http://www.environment.fi/download.asp?contentid=116835&lan=fi

Bloomfield, S.F. 2002. Significance of biocide usage and antimicrobial resistance in domiciliary environments, *Journal of Applied Microbiology Symposium Supplement*, **92** pp. 144–157.

Carter, W. P. L. 2009. Updated Maximum Incremental Reactivity Scale for Regulatory Applications Prepared for California Air Resources Board Contract 07-339, College of

Engineering Center for Environmental Research and Technology, University of California, Riverside, CA 92521. 64 p.

[CEN] European Committee for Standardization. 2006a. Paints and varnishes – Laboratory method for testing the efficacy of film preservatives in a coating against fungi. CEN / TC 139 pr EN 15457: 2006. 8 p.

[CEN] European Committee for Standardization. 2006b. Paints and varnishes – Laboratory method for testing the efficacy of film preservatives in a coating against algae. CEN / TC 139 pr EN 15458: 2006. 9 p.

Chirban, J. T., 1996. Interviewing in Depht: *The interactive-relational approach,* SAGE Publications Ltd, USA, pp. 37-57.

Colborn, T., vom Saal, F. S. and Soto, A. M. 1993.Developmental Effects of Endocrine Disrupting Chemicals in Wildlife and Humans, *Environmental Health Perspectives* **101** 5, pp. 378-384.

[CTFA] Cosmetics, Toiletries, and Fragrance Association 2001. Determination of Preservation Adequacy of Water-Miscible Cosmetic and Toiletry Formulations. *CTFA Technical Guidelines.* Washington, DC: Cosmetics, Toiletries, and Fragrance Association, Inc. 8 p.

Denyr, S. P. and Maillard, J-Y. 2002. Cellular impermeability and uptake of biocides and antibiotics in gram – negative bacteria, *Journal of Applied Microbiology Symposium Supplement*, **92** pp. 35-45.

[EC] European Commission. 1995. Directive No 95/2/EC of 20 February 1995 on food additives other than colours and sweeteners 20 OJ L **61**, pp. 1-40.

[EC] European Commission. 1998. Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on the market. O J L **123**, pp. 1-63.

[EC] European Commission. 1999. Directive 1999/45/EC of the European Parliament and of the Council of 31 May 1999 concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labeling of dangerous preparations. OJ L **200** pp. 1-78.

[EC] European Commission. 2002a. Directive 2002/95/EC of the European Parliament and of the Council of 27 January 2003 on the Restriction of the use of certain Hazardous Substances (RoHS) in electrical and electronic equipment. OJ L **37** pp.19-23

[EC] European commission. 2002b. Directive 2002/96/EC of the European Parliament and of the Council of 27 January 2003 on waste electrical and electronic equipment (WEEE).OJ L **37** pp. 24-38.

[EC] European Commission. 2003a. Directive 2003/53/EC of the European Parliament and of the Council of 18 June 2003 amending for the 26th time Council Directive 76/769/EEC relating to restrictions on the marketing and use of certain dangerous substances and preparations (nonylphenol, nonylphenol ethoxylate and cement) OJ L **178** pp. 24-27.

[EC] European Commission. 2003b. Commission Regulation (EC) No 2032/2003 of 4 November 2003 on the second phase of the 10-year work programme referred to in Article 16(2) of Directive 98/ 8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market, and amending Regulation (EC) No 1896/2000. OJ L **307** pp. 1-180

[EC] European Commission. 2003c. Commission Recommendation of 10 July 2003 on guidance for the implementation of Regulation (EC) No 761/2001 of the European Parliament and of the Council allowing voluntary participation by organisations in a Community eco-management and audit scheme (EMAS) concerning the selection and use of environmental performance indicators. OJ L **184** pp19-32.

[EC] European Commission. 2003d. Directive 2003/15/EC of the European Parliament and of the Council of 27 February 2003 amending Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products. OJ L **66** pp. 26-35.

[EC] European Commission. 2003e. Technical Guidance Document on Risk Assessment *in support of* Commission Directive 93/67/EEC on Risk Assessment for new notified substances Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market Part 1. Office for Official Publications of the European Communities, Luxembourg.

[EC] European Commission. 2004. Directive 2004/42/EC of the European Parliament and of the Council of 21 April 2004 on the limitation of emissions of volatile organic compounds due to the use of organic solvents in certain paints and varnishes and vehicle refinishing products and amending Directive 1999/13/EC. O J L **143** pp 87-96.

[EC] European Commission. 2005. Directive 2005/90/EC of the EUROPEAN Parliament and of the Council of 18 January 2006 amending, for the 29th time, Council Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations (substances classified as carcinogenic, mutagenic or toxic to reproduction — c/m/r) OJ **33** pp. 28-81.

[EC] European Commission. 2006a. Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council

Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. OJ L **137** pp. 1-280.,

[EC] European Commission. 2006b. Guidance Document for the implementation of the European PRTR. Available at: http://ec.europa.eu/environment/air/pollutants/stationary/eper/pdf/en_prtr.pdf (Accessed 11.1.2011)

[EC] European Commission. 2008a. Council Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). O J L **142** pp 1-739.

[EC] European Commission. 2008b. Commission Decision of 13 August 2008 establishing the ecological criteria for the award of the Community eco-label to indoor paints and varnishes. Available at. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:181:0039:0048:EN:PDF. (Accessed 11.1.2011).

[EC] European Commission. 2008c. Table 3.1. to Annex VI of CLP regulation. Harmonised classification of the hazardous substances. Available at: http://ec.europa.eu/enterprise/sectors/chemicals/files/ghs/w_annex_vi_table_3_1_en.doc (Accessed 11.1. 2011).

[EC] European Commission. 2008d. Directive 2008/98/EC of the European Parliament and of the Council of 19 November 2008 on waste and repealing certain Directives. OJ L **312** pp. 3-30.

[EC] European commission. 2008e. REGULATION (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labeling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 OJ L pp**. 353** 1-1355.

[EC] European commission. 2008f. DIRECTIVE 2008/105/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 2008 on environmental quality standards in the field of water policy, amending and subsequently repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC of the European Parliament and of the Council. OJ L 348 84-97.

[EC] European Commission 2009a. EU action on pesticides. European Commission, Brussels, Belgium ISBN 978-92-79-11599-8. Available at: http://ec.europa.eu/food/plant/protection/evaluation/docs/factsheet_pesticides_en.pdf (Accessed 3.1.2011).

[EC] European Commission 2009b. Proposal for a Regulation of the European parliament

and of the council concerning the placing on the market and use of biocidal products. CO M(2009) 267 final 2009/0076 (COD ) Brussels.

[EC] European Commission. 2010a. What is the Ecolabel? http://ec.europa.eu/environment/ecolabel/about_ecolabel/what_is_ecolabel_en.htm (Accessed 11.1. 2011).

[EC] European Commission. 2010b. Biocides: Substances included in Annex I or IA to Directive 98/8/EC. Available at: http://ec.europa.eu/environment/biocides/ annexi_and_ia.htm (Accessed 3.1.2011).

[EC] European Commission. 2010c. Buying Social - A Guide to Taking Account of Social Considerations in Public Procurement. Luxembourg: Publications Office of the European Union.

[ECHA] European CHemicals Agency. 2008. Guidance on information requirements and chemical safety assessment Part C: PBT Assessment. Available at: http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_part_c_en.pdf?vers=20_08_08 (Accessed 3.1.2011)

[ECHA] European CHemicals Agency. 2009. Guidance on the Application of the CLP Criteria. Available at:

http://guidance.echa.europa.eu/docs/guidance_document/clp_en.pdf. (Accessed 3.1.2011)

[ECHA] European CHemicals Agency. 2010. Candidate List of Substances of Very High Concern for authorization. Available at: http://echa.europa.eu/chem_data/authorisation_process/candidate_list_table_en.asp (accessed 3.1.2011)

[EEA] European Environment Agency. 2009.E-PRTR The European Pollutant Release and Transfer Register, European Environment Agency, Copenhagen, Available at: http://prtr.ec.europa.eu/PollutantReleases.aspx. (Accessed 3.1.2011)

[EEC] European Economic Community. 1976. COUNCIL DIRECTIVE of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products 76/768/EEC. OJ L **262** p..169 -200.

[EEC] European Economic Community. 1981. 81/437/EEC: Commission Decision of 11 May 1981 laying down the criteria in accordance with which information relating to the inventory of chemical substances is supplied by the Member States to the Commission. OJ L **167** p.31 -38.

[EEC] European Economic Community. 1991. Council directive 91/414/EEC. OJ L **230,** pp. 1-32.

Fernandez-Redondo, V., Beiras-Fernandes, A. and Toribo, J. 2004: Occupational Dermatitis in a milk industry worker due to Kathon CG, *Dermatitis* **15** pp. 73-74.

Finkel, A. M. and Ryan, P. B., Risk in the workplace. 2007. Where Analysis Began and Problems Remain Unsolved In: Robson, M and Toscano, W. (Ed.), *Risk assessment for environmental health*. John Wilay & Sons, Inc. San Francisco, pp. 187-237.

Fisher, G. 1964. Award Ceremony Speech. Available at : http://nobelprize.org/nobel_prizes/medicine/laureates/1948/press.html (Accessed 3.1.2011).

Frohwein, T. and Hansjürgens, B. 2005. Chemicals regulation and the Porter Hypothesis : a critical review of the new European chemicals regulation. *Journal of Business Chemistry*, **2**(1) pp. 19-36.

[FTS] Fair Trade Standards. 2009. Aims of the Fair Trade Standards. Cited 2010 June 8th. Available at: http://www.fairtrade.net/aims_of_fairtrade_standards.html. (Accessed 3.1.2011).

Gilbert, P., D.G. Allison and A.J. McBain. 2002. Biofilms in vitro and in vivo: do singular mechanisms imply cross-resistance? *Journal of Applied Microbiology Symposium Supplement* **92**, pp. 98–110.

Gorham E., 1982. Robert Angus Smith, F.R.S., and 'Chemical Climatology' *Notes & Records of the Royal Society* **36**, pp. 267-272. http://rsnr.royalsocietypublishing.org/content/36/2/267 (Accessed 3.1.2011)

Guidotti, T. L. and Moses, S. M. 2007. Toxicological basis for risk assessment In: Robson, M and Toscano, W. (Ed.), *Risk assessment for environmental health*. John Wilay & Sons, Inc. San Francisco, pp. 55-84.

Hall, G. M. and Howe, J. 2010. Sustainability of the chemical manufacturing industry—Towards a new paradigm? *Education for Chemical Engineers,* **5** 4, pp 100-107.

Hartung, T. and Rovida, C. 2009. Chemical regulators have overreached. *Nature* **460** (27) pp. 1080-1081.

Hashash, S. 2009. 'Green' lightbulbs poison workers, *The Sunday Times* May 3, Times Newspapers Ltd, London.

Hauber, C. 2005. Microbicide applications in the leather industry In: Paulus, W., (Ed.), Directory of microbicides for the protection of materials, New York, Springer, pp. 317-324.

Hirsjärvi, S., Remes, P. and Sajavaara, P. 2000. *Tutki ja kirjoita,* 6. edition. Tummavuoren kirjapaino Oy, Vantaa, pp. 194-197.

Hirsjärvi, S and Hurme, P. 1993. *Teemahaastattelu*, 6. edition. Yliopistopaino, Helsinki, 144 p.

Holland, M. and Pye, S. 2006. An update on cost-benefit analysis of the CAFÉ programme AEA Technology AEAT/ ED48763001/CAFE-CBA update, November 2006. Issue 2. Environment Didcot, United Kingdom. 14 p.

Hutchinson, G. E. 1969. Eutrophication past and present in: *Eutrophication: Causes, Consequences, Correctives. Proceedings of Symposium*, National Academy of Science, Washington D. C. pp. 17-28.

[IBRG] International Biodeterioration Research Group. 2000. A Method for Evaluating the Resistance of Water-Based Paints to Bacterial Growth in the Wet-Stage – Draft 9, November, IBRG P00/009.1. (unpublished data) 19 p.

[IBRG] International Biodeterioration Research Group, 2009. Available at http://www.ibrg.org/. (Accessed 2.9.2009).

[ICCA] International Council of Chemical Associations. 2008. Responsible Care status report 2008. Available at:http://www.responsiblecare.org/filebank/Status%20Report%2001_05.pdf (Accessed 3.1.2011).

[IMO] International Maritime Organization. 2002. Anti-fouling systems, London, United Kingdom. Available at: http://www.imo.org/OurWork/Environment/Anti-foulingSystems/Documents/FOULING2003.pdf (Accessed 3.1.2011).

[ISO] International Standardisation Organisation. 2004. ISO 14001 : 2004. Environmental Management Standard. 32 p.

Kerin, R. A., Varadaran, P. R. and Peterson, R. A. 1992. Firs-Mover Advantage ; A Synthesis, Conseptual Framework and Research Propositions. Journal of Marketing. **56**, pp. 33-52.

Kähkönen, E, Nodström, K. and Suominen M. 2007. A challenge for biocides – Achieving long-term protection for colorants in point of sale dispensers. *European Coatings Journal* **7-8**, pp. 28-33.

Kähkönen E. and Nordström K. 2008. Toward a Nontoxic Poison: Current Trends in (European Union) Biocides Regulation, *Integrated Environmental Assessment and Management* **4**(4) pp. 471–477.

Kähkönen, E., Soirinsuo, K and Nordström, K. 2010.Trends in EU Biocides Regulation, *Chemistry today*. **28** (2) pp. 19-22.

Kähkönen, E., Hirvonen, T. and Nordström, K. 2010. New biocide active substances: needs and challenges in the EU as viewed by industry. *Journal of Business Chemistry* **7**(2) pp. 69-79.

Lewis, J. 1985. The birth of EPA. *EPA-Journal,* November 1985. Available at: http://www.epa.gov/history/topics/epa/15c.htm. (Accessed 3.1.2011).

Lindner, W. 2005. Surface coatings. In: Paulus, W., (Ed.), *Directory of microbicides for the protection of materials*, New York, Springer, pp. 347-376.

Lindner, W. 2007. Dry-film preservation: BCM for exterior coatings – past, presence, future. *Proceedings in European Coatings Conference "Novel biocide technology 3*", Vinsenz Network, Hannover.

Ludensky, M. 2005. Microbiological control in cooling water systems In: Paulus, W., (Ed.), *Directory of microbicides for the protection of materials*, New York, Springer, pp. 121-140.

Maier, L. E., Lampel, H. P, Bhutani, T. and Jackob, S. E. 2009. Hand Dermatitis : a focus on allergic contact Dermatitis to biocides. *Dermatologic clinics* **27** (3), pp. 251-264.

Maillard J.-Y. 2002.Bacterial target sites for biocide action, *Journal of Applied Microbiology Symposium Supplement* **92**, pp. 16–27.

Manson, J. 1996. Qualitative Researching, SAGE Publications Ltd, London, pp. 35-55, 107-172.

Mattila, T. and Antikainen, R. 2010. Muut elinkaarijohtamista tukevat menetelmät In: Antikainen R (Ed.), *Elinkaarimetodiikkojen nykytila, hyvät käytännöt ja kehitystarpeet* (in Finnish). Suomen ympäristökeskuksen raportteja 7/2010, 83 s, Suomen ympäristökeskus (SYKE). ISBN: 978-952-11-3734-1 (PDF). Available at: http://www.environment.fi/download.asp?contentid=116835&lan=fi pp. 62-72.

Miller, D. C. and Salkind. 2002. N. J., *Handbook of Research Design & Social Measurement*, 6. edition, SAGE Publications Inc, California, p. 162, 164.

Monroe, S. and Polk, R. 2000. Antimicrobial use and bacterial resistance. **3** pp. 496–501.

[NE] Nordic Ecolabelling. 2008. Nordic Ecolabelling of Indoor paints and varnishes. Version 2.0 • 4 November 2008 – 31 December 2012. Available from http://www.svanen.nu/sismabmodules/criteria/getfile.aspx?fileid=105029001. (Accessed 3.1.2011).

Nystén, A. 2008. *Kemikaalikimara,* Teos, Helsinki. 266 p.

o'Driscoll, J. B. and Beck, M. H. 1988. Occupational allergic contact dermatitis from Kathon WT. *Contact dermatitis*. **19**(1) p. 63.

[OECD] Organization of Economic Co-operation and Development. 2007. Report on the Regulatory Uses and Applications in OECD Member Countries of (Quantitative) Structure-Activity Relationship [(Q)SAR] Models in the Assessment of New and Existing Chemicals Http://Www.Oecd.Org/Dataoecd/55/22/38131728.Pdf (Accessed 3.1.2011).

[OECD] Organisation of Economic Co-operation and Development. 2010. OECD Screening Information DataSet (SIDS) High Production Volume Chemicals (Processed by UNEP Chemicals). Available from http://www.inchem.org/pages/sids.html. (Accessed 15.4.2010).

[OHSAS] Occupation Health and Safety Assessment Series. 2011. OHSAS 18001, Health & Safety Standard. Available from http://www.ohsas-18001-occupational-health-and-safety.com/what.htm (Accessed 3.1.2011).

Passman, F. J., 1995. Formaldehyde risk in perspective: a toxicological comparison of twelve biocides. *Journal of the society of tribologists and lubrication engineering*. **52**, 1 pp. 69-80.

Pesonen, T. 2011. Mikrobiologisen laadun varmennus kosmetiikkatuotteen kehitysprosessissa / Quality assurance of Microbiological safety in the Development Process of a New Cosmetic Product (in Finnish). Master's thesis. In press. Otaniemi. 92 p.

Pitts, J. N. Jr. and Stephens, E. R. 1978. Arie Jan Haagen-Smit. *Journal of Air Pollution Control Association*, **28** 5 pp. 16-17.

[RAL] RAL-Deutsches Institut für Gütesicherung und Kennzeichnung. 2010a. Basic Criteria for Award of the Environmental Label Low-Emission Wall Paints RAL-UZ 102, Edition April 2010. RAL GmbH Sankt Augustin, Germany. Available at: http://www.blauer-engel.de/en/products_brands/vergabegrundlage.php?id=6 (Accessed 3.3.2011).

[RAL] RAL-Deutsches Institut für Gütesicherung und Kennzeichnung**.** 2010b. Appendix 1 to the Basic Criteria RAL-UZ 102. Pot Preservation. http://www.blauer-engel.de/_downloads/vergabegrundlagen_en/102-1004-Appendix-1.pdf . (Accessed 3.3.2011).

[RAL] RAL-Deutsches Institut für Gütesicherung und Kennzeichnung**.** 2010. The Blue Angel – Eco-Label with Brand Character. http://www.blauer-engel.de/en/blauer_engel/index.php (Accessed 3.1.2011).

[RH], Rohm&Haas SA. 2004. Rocima 523 Käyttöturvallisuustiedote (Material Safety Data Sheet). Rohm&Haas.

Robbins, J. and Levy, R. 2005. A review of the microbiological degradation of fuel. In: Paulus, W., (Ed.), *Directory of microbicides for the protection of materials*, New York, Springer, pp. 177-201.

Russel A. D. 2002. Mechanisms of antimicrobial action of antiseptics and disinfectants; an increasingly important area of investigation, *Journal of antimicrobial Chemotherapy* **49** 597-599.

Stake, R. E. 1995. *The Art of Case Study Research* SAGE Publications Inc, California, pp. 1-4

Scholtyssek, R. 2005. Protection of cosmetics and toiletries. In: Paulus, W., (Ed.), *Directory of microbicides for the protection of materials,* New York, Springer, pp. 263-286.

Schulte, S. Wingender, J. and Flemming, H.-C. 2005. Efficacy of biocides against biofilms. In: Paulus, W., (Ed.), *Directory of microbicides for the protection of materials*, New York, Springer, pp. 93-120.

Soirinsuo,K., Kähkönen, E. and Nordström. K. 2009. Feasibility of Active Ingredient (AI) Development for New Biocides in the EU. *Journal of Business Chemistry* **6**(3) pp. 128-136.

Tebert, C.; Volz, S.; Terwoert, J.; Klotz, V.; Müller, W.; Theloke, J.; Vencovsky, D.; Fleet, D. and Kallay. T. K. 2009. Implementation and Review of Directive 2004/42/EC. Final Report – Part 1: Main Report, Annexes 1-25. Ökopol GmbH Institute for Environmental Strategies Hamburg. Germany. 546 p.

Tellis, W. 1997. Introduction to the Case Study, *The Qualitative Report*, **3**(2) Available: http://www.nova.edu/ssss/QR/QR3-2/tellis1.html. (Accessed 11.1. 2011).

[UN] United Nations. 1987. Our Common Future, Chapter 2: Towards Sustainable Development World Commission on Environment and Development A/42/427. Geneva, Switzerland.

[UNEP] United Nations Environment Programme. 2009. *Handbook for the Montreal Protocol on Substances that Deplete the Ozone Layer* 8th edition. United Nations Environment Programme PO Box 30552 Nairobi Kenya. Available at: http://www.unep.ch/ozone/Publications/MP_Handbook/MP-Handbook-2009.pdf. (Accessed 11.1. 2011).

Walsh, S. E. 2003. Development of bacterial resistance to several biocides and effects on antibiotic susceptibility, *Journal of Hospitals Infection* **55** pp. 98-107.

[WHO] World Healt Organization. 2001. Global Strategy for Containment of Antimicrobial Resistance. WHO, Switzerland. Available at: http://whqlibdoc.who.int/hq/2001/WHO_CDS_CSR_DRS_2001.2.pdf (accessed 30.8.2011). 100 p.

Williams, G.R. 2005. Industrial wood protection. In: Paulus, W., (Ed.), *Directory of microbicides for the protection of materials*, New York, Springer, pp. 419-439.

Yin, R. K. 1981. The Case Study Crisis: Some Answers, *Administrative Science Quarterly*, **26**(1), pp. 58-65.

# PUBLICATIONS

Reduction of chemical risk in our environment is common goal for the authorities, who develop the guidance for the industry, and for the industry, which develops the products and processes to meet the requirements. However, both parties meet dilemmas here; the authorities need to keep the development of safer chemicals profitable while enforcing the costly animal test requirements for the new chemicals. The chemical industry, in turn, will need to find the optimal product compositions and raw-material sources, which minimize, on one hand, chemical and microbial risks and, on the other hand, occupational and environmental risks. The solutions lie in the development of cost-efficient tools to assess chemical risks e.g. in vitro tests, cost-efficient methods for choosing optimal tools to control microbial risks. Finally, improved education on chemical risk for those responsible for chemical product development and raw-materials buying is needed.

Aalto-DD 96/2011

ISBN 978-952-60-4316-6 (pdf)
ISBN 978-952-60-4315-9
ISSN-L 1799-4934
ISSN 1799-4942 (pdf)
ISSN 1799-4934

**Aalto University**
**School of Chemical Technology**
**Department of Biotechnology and Chemical Technology**
**www.aalto.fi**

BUSINESS + ECONOMY

ART + DESIGN + ARCHITECTURE

SCIENCE + TECHNOLOGY

CROSSOVER

**DOCTORAL DISSERTATIONS**