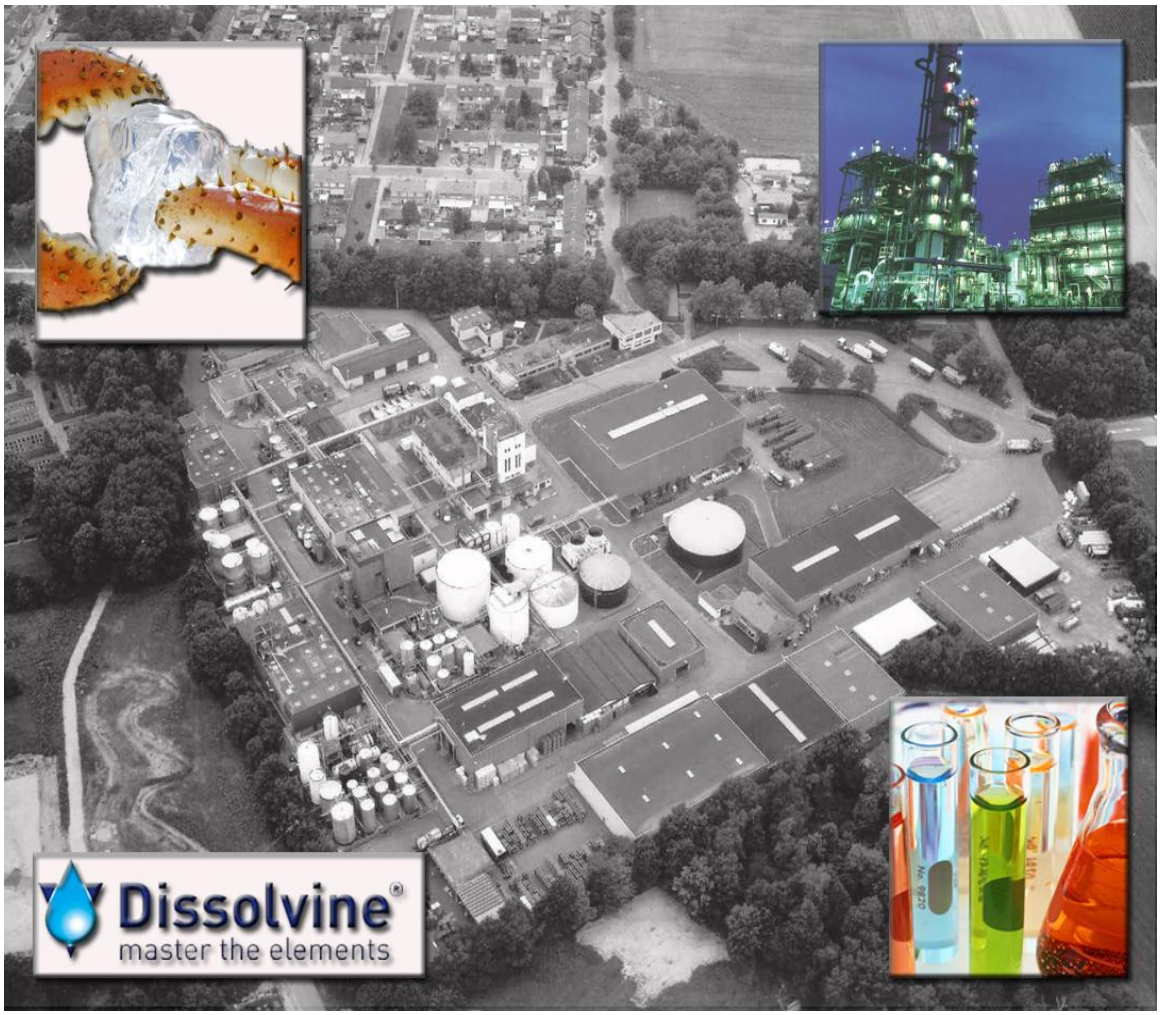
SAFE USE OF CHEMICALS IN THE SUPPLY CHAIN

How to fulfill the duties of a legal entity, acting both as an importer and an industrial downstream user, regarding to raw materials as mentioned in REACH, as efficient and effective as possible in a unequivocal way.



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Master of Science thesis
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Je kunt wel hard lopen, maar dat betekent nog niet dat je ook echt vooruitgang boekt. (*vertaald oud brabants gezegde*)

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SAFE USE OF CHEMICALS IN THE SUPPLY CHAIN:
How to fulfill the duties of a legal entity, acting both as an importer and an industrial downstream user, regarding to raw materials as efficient and effective as possible in a univocal way.

VEILIG GEBRUIK VAN CHEMICALIëN IN DE KETEN:
Hoe kan een juridische entiteit, die opereert als zowel een importeur als een industriële downstream-gebruiker, voldoen aan de verplichtingen voortvloeiend uit REACH met betrekking tot de grondstoffen, die zij gebruikt, en hoe kan dit zo efficiënt en effectief mogelijk en op een eenduidige manier gedaan worden?

Cover photo: Overview of Akzo Nobel Functional Chemicals bv, Herkenbosch [Paul Hoedenmaekers Fotografie]

PREFACE

My whole working life revolves round three key concepts: the environment, labour circumstances and chemistry. In the companies where I was employed, I have therefore always tried, to achieve a high level of safety for men and environment, without reducing the competitiveness of the companies involved.

As Manager Health, Safety and Environment at a chemical production plant, I came in a very early stage into contact with interesting aspects regarding REACH. Aspects, which nowadays still should be considered as an unexplored area.

Just as a hobby, I started a MSc study Environmental Science at the Open University The Netherlands. Initially I was very positive and enthusiastic, but I must admit, it is absolutely not easy to complete an university study besides a regular job that requires well over 40 hours per week.
And then it's nice to have such an interesting phenomenon as REACH occurring as potential thesis topic. So it works both ways.
This is the reason why I have chosen some parts of this topic as a subject for my graduate project.
My journey to explore this subject was a very interesting one, more than I was aware of before, although it was not always easy and/or pleasant, and, added to this, it took a lot of my scarce spare time.
And now, after years of browsing in the scientific world, thinking and dreaming of REACH and later on finishing my MSc thesis, it is time to dedicate my spare time to some old and almost forgotten hobbies.

Composition of the examination committee regarding this MSc thesis
For the assessment of this graduate subject and the including MSc thesis, an examination committee was established, consisting of:

Mr. Prof. Lucas Reijnders PhD	chairman of the committee and tutor, Open University The Netherlands
Mr. Pieter Geluk MSc	secretary of the committee, Open University The Netherlands
Mrs. Cobi de Blécourt-Maas MSc	2nd tutor, Open University The Netherlands
Mr. Nol van der Steen PhD	external member, Akzo Nobel Functional Chemicals bv, Amersfoort, The Netherlands

Acknowledgements
Realizing and accomplishing of this MSc thesis could never have been possible without the unquestioning and continuing support of a considerable number of people, which I would like to thank all warmly.
I know that none of them would appreciate to read their names here in capital.
First of all, I start to thank all those anonymi, including my family and friends, because the main support and encouragement came from members of this group! They have supported me in every way in difficult times, dragged me through depressions and later on they have helped me back on my feet again.
One exception: a special word of thanks to my beloved sons Robbert & Pepijn for doing all their odd jobs.

Value support and scientific input was provided by my colleagues of AkzoNobel and other experts within the dutch chemical industry. Thanks a lot to all!

Priceless was the help I received from my colleagues Ingrid van den Heuvel and Nicole Otten for the corrections in the text of this MSc thesis and the design of the lay out of it.

To my employer, Akzo Nobel Functional Chemicals B.V., owner of a small but very important production site based in a nice village called Herkenbosch which is situated in the southern part of the Netherlands, I am also greatly indebted.

Last but surely not least I would like to thank my tutors Lucas Reijnders and Cobi de Blécourt-Maas and the extern member of the examination committee and AkzoNobel colleague Nol van der Steen for their enthusiasm, encouragement, critical comments, valuable discussions and scientific input which helped me a lot in creating this MSc thesis.

Beegden,
March, 19, 2010
Laurens Maatman

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LIST OF USED ABBREVATIONS AND TYPICAL NOMENCLATURE

ANFCH:	Akzo Nobel Functional Chemicals B.V., site Herkenbosch
ASTM:	American Society for Testing and Materials, one of the largest voluntary standards development organizations in the world.
BNP	Bedrijfsnoodplan, in english: Site Emergency Plan
BRZO'99:	Besluit Risico's Zware Ongevallen 1999 (dutch post Seveso legislation)
Chelates:	Chemicals that form soluble, complex molecules with certain metal ions, inactivating the ions so that they cannot normally react with other elements or ions to produce precipitates or scale." [according to ASTM-A-380] The formation or presence of bonds (or other attractive interactions) between two or more separate binding sites within the same ligand and a single central atom. A molecular entity in which there is chelation (and the corresponding chemical species) is called a 'chelate' [according to IUPAC].
CRM:	Carcinogenic, reprotoxic and mutagenic substances
CSA:	Chemical Safety Assessment
CSR:	Chemical Safety Report
DCS:	automated process control system
Dissolvine®:	the Akzo Nobel brand name for products known as chelates
DNEL:	Derived No-Effect-Level
DTPA:	Diethylenetriaminepentaacetic acid
DU:	Downstream user
ECHA:	European Chemicals Agency
EDA:	Ethylene diamine
EDG:	Ethanoldiglycinic acid
EDTA:	Ethylenediaminetetraacetic acid
EDTN:	Ethylenediaminetetraacetonitrile
EINECS:	European Inventory of Existing Commercial Chemical Substances
ELINCS:	European List of Notified Chemical Substances
ES:	Exposure Scenario
EU:	European Union
GLDA:	Glutamic acid, N, N-diacetic acid
Glucoheptonate:	Glucoheptonic acid
HEDTA:	Hydroxyethylethylenediaminetriacetic acid
HSE:	Health, Safety and Environment
IPCS:	International Programme on Chemical Safety
IRA:	Integrated Risk Assessment
ITS:	Integrated Testing Strategies
IUCLID:	International Uniform Chemical Information Database
IUPAC:	International Union of Pure and Applied Chemistry IUPAC nomenclaturel is a system of naming chemical compounds and of describing the science of chemistry in general. It is developed and kept up to date under the auspices of the IUPAC.
LLNA:	Local Lymph Node Assay test for skin sensitisation
MDHS:	Methods for the Determination of Hazardous Substances
NEN:	Nederlands Normalisatie instituut
NIOSH:	National Institute for Occupational Safety and Health
NTA:	Nitriloacetic acid
OECD HPV:	Organisation for Economic Co-operation and Development High Production Volume
OECD SIDS:	OECD Screening Information Data Set
OECD SIDS SIAR:	OECD SIDS Initial Assessment Report
PBT:	Persistent, Bio-accumulative, Toxic substances
PDTA:	1,3-Propylenediaminetetraacetic acid
PDTN:	Propylenediaminetetraacetonitrile
PEC:	Prognosticated Concentration of a chemical in the Environment
PNEC:	Predicted No-Effect-Concentration
PPE:	Personal Protection Equipment

PRA:	Probalistic Risk Assessment
PR:	(in dutch: Plaatsgebonden Risico, in english: Individual Risk) Individual risk is defined as the annual probability that an unprotected, individual, that is constantly present at a given location, dies due to an accident at a hazardous site.
QRA:	Quantitative Risk Analysis
QSAR:	Quantitative Structure-Activity Relationships
RA:	Regulatory Affairs
RCR:	Risk Characterization Ratio
REACH:	acronym for: **R**egistration, **E**valuation, **A**uthorization and Restriction of **Ch**emicals
RMM:	Risk Management Measures
SCC:	Strictly Controlled Conditions
SDS:	Safety Data Sheet
Singer synthesis:	The two-step Singer synthesis is the only commercial process currently used to manufacture EDTA that uses HCN as a raw material. The Singer synthesis has two separate steps,the cyanomethylation step and hydrolysis. In cyanomethylation, hydrogen cyanide and formaldehyde react with ethylenediamine to form insoluble (ethylenedinitrilo)tetraacetonitrile (EDTN). The intermediate nitrile is then separated, washed, and hydrolyzed with sodium hydroxide to tetrasodium EDTA. Ammonia is liberated as a byproduct.
STEL:	Short-Term Exposure Limit (STEL) The STEL is the *concentration* to which it is believed that workers can be *exposed* continuously for a short period of time [usually a 15 minute reference period] without suffering from 1) irritation, 2) *chronic* or irreversible tissue damage, or 3) *narcosis* of sufficient degree to increase the likelihood of accidental injury, impair self rescue or materially reduce work efficiency, and provided that the daily TWA is not exceeded.
Strecker synthesis:	The Strecker amino acid synthesis, devised by Adolph Strecker, is a series of chemical reactions that synthesize an amino acid from an aldehyde (or ketone). The aldehyde is condensed to form an α-aminonitrile, which is subsequently hydrolyzed to give the desired amino-acid.
SVHC:	Substance of Very High Concern
TWA:	Time weighted Average (TWA) The TWA is the *time-weighted average concentration* for a conventional 8-hour workday and a 40-hour workweek, to which it is believed nearly all workers may be repeatedly *exposed*, day after day, without *adverse effect*. They are usually expressed in units of ppm (volume/volume) or mg/m3.
UNEP:	United Nations Environment Programme
vPvB:	substances that are very Persistent, very Bio-accumulative
WHO:	World Health Organisation

SUMMARY

Chemicals are an essential element in our society. They are incorporated into many products such as toys, medicines, clothing, detergents, etc. and play a very important role in the economy.
The former EU legislative framework for chemical substances was a patchwork of different Directives and Regulations which had developed historically. It was introduced under regulation (EC) 793/93.
REACH, an acronym for: **R**egistration, **E**valuation, **A**uthorization and Restriction of **Ch**emicals, is the new EU legislative framework for chemical substances, which became effective 1st of June 2007.
The aims of REACH are to:

- Improve the protection of human health and the environment from the risks that can be posed by chemicals
- Enhance the competitiveness of the EU chemicals industry, a key sector for the economy of the EU.
- Promote alternative methods for the assessment of hazards of substances
- Ensure the free circulation of substances on the internal market of the European Union

In principle, REACH applies to all chemicals: not only chemicals used in industrial processes but also those in our day-to-day life, e.g. in cleaning products, paints and in articles intended for consumer use such as clothes, furniture and electrical appliances. REACH concerns all companies that deal with chemicals.
Unlike in the past, REACH places greater responsibility on the industry to manage the risks that chemicals may cause to health and environment and to provide appropriate safety information for professional users and, as far as the most hazardous substances are concerned, also for consumers.

With this in mind, this MSc thesis is aiming to give an adequate answer to the question:

> *How to fulfill the duties of a legal entity, acting both as an importer and an industrial downstream user, regarding to raw materials, as mentioned in REACH, as efficient and effective as possible in a unequivocal way?*

In order to answer this question, four research questions were formulated. These research questions were further elaborated on the basis of two examples, the raw materials formaldehyde and nitriles.
First, a literature search was conducted to collect the necessary legal, toxicological, process-technological and environmental information.
The legal findings showed that in certain specific situations there is the possibility to register a raw material as a “transported isolated intermediate”.
Some of the chemical processes at the site Herkenbosch of Akzo Nobel Functional Chemicals B.V. were then analyzed as to the potential compliance with the legal obligations concerning REACH, using the possibility of registration of a raw material as a “transported isolated intermediate”.
Process conditions and potential exposure of employees as a result of the use of these raw materials were established.
Subsequently, the uncertainties in the chosen method and the results that were found, were further investigated and discussed, based on REACH legislation and some recent articles in the literature.
Finally all results were reviewed on their merits, discussed and conclusions were drawn.

Conclusions

It has been proven that it is possible to fulfill the duties of both a registrant and a downstream user and their mutual activities and communication regarding REACH in an efficient, effective and unequivocal way for the raw materials formaldehyde and nitriles at the site Herkenbosch of Akzo Nobel Functional Chemicals B.V..

By means of the approach of registration of a, for that purpose qualified, raw material as a “transported isolated intermediate”, a registrant can provide reduced registration information according to Article 18 (2) if this registrant confirms or states that he has received confirmation from both the manufacturer/importer and the user (being in the EU or outside the EU), that the substance is manufactured and used under strictly controlled conditions (SCC’s) as described under Article 18 (4).
In that case both the registrant and the user are each liable for their own statement regarding the SCC’s.

Benefits

The approach studied here:

- Is *fully in compliance* with REACH [see art. 18(2) & 18(4)] and other legislation.
- Is valid for *all substances* provided that the obligations of REACH art. 18(2) & 18(4) are fully met so it can also be applied for “substances of very high concern” such as CRM’s, PBT’s and vPvB’s.
- Is as *efficient and effective* as possible with respect to the concerning application and, moreover, is *unequivocal*.
- Is *very feasible* and *affiliates to other duties* in the domain of HSE and RA..
- Demands relatively limited efforts of registrant, downstream user and authorities and entails relatively low costs.
- The above mentioned means that, given the situation and the practices at the site Herkenbosch, ANFCH could successfully use this method for many of its raw materials. On the analogy of this, the same is valid for a significant proportion of the raw materials of a considerable part of the chemical industry.
  However, it should be proven every time, for each raw material, that this substance is manufactured and used under strictly controlled conditions (SCC’s) as described under REACH Article 18 (4),

SAMENVATTING

Chemicaliën zijn een essentieel element in onze samenleving. Zij bevinden zich in veel producten, zoals speelgoed, medicijnen, kleding, wasmiddelen, etc., en vervullen een zeer belangrijke rol in de economie. Het voormalige kader voor de EU-regelgeving voor chemische stoffen, dat vanaf 1993 tot stand was gekomen, was een grote lappendeken van richtlijnen en verordeningen, en was ook weinig effectief. REACH, een acroniem voor **R**egistratie, **E**valuatie, **A**utorisatie en beperking van **Ch**emicaliën, is op 1 juni 2007, als het nieuwe kader voor de EU-regelgeving voor chemische stoffen, in werking getreden. De doelstellingen van REACH zijn:

- verbeteren van de bescherming van de menselijke gezondheid en het milieu tegen de risico's, die kunnen worden veroorzaakt door chemische stoffen
- verbeteren van het concurrentievermogen van de Europese chemische industrie, een belangrijke sector voor de economie van de EU.
- bevorderen van alternatieve methoden voor de beoordeling van de gevaren van (chemische) stoffen
- waarborgen van het vrije verkeer van stoffen op de interne markt van de Europese Unie

In principe geldt REACH voor alle chemische stoffen: niet alleen voor chemicaliën die gebruikt worden in industriële processen, maar ook die in ons dagelijks leven, bijv. die in schoonmaak-middelen, verf en die in voorwerpen die bestemd zijn voor gebruik door de consument, zoals kleding, meubels en elektrische apparaten.
Alle bedrijven die met chemische stoffen omgaan, hebben derhalve met REACH te maken. Anders dan in het verleden legt REACH een veel grotere verantwoordelijkheid bij de industrie daar waar het gaat om het beheersen van de risico's van chemische stoffen en het verstrekken van adequate informatie over het veilig gebruik ervan aan professionele gebruikers en, voor zover het de meest gevaarlijke stoffen betreft, ook aan de consument.

Met dit in het achterhoofd, tracht deze MSc-thesis een adequaat antwoord te geven op de vraag:

Hoe kan een juridische entiteit, die opereert als zowel een importeur als een industriële downstream-gebruiker, voldoen aan de verplichtingen voortvloeiend uit REACH met betrekking tot de grondstoffen, die zij gebruikt, en hoe kan dit zo efficiënt en effectief mogelijk en op een eenduidige manier gedaan worden?

Ter beantwoording van deze vraag werd een viertal onderzoeksvragen geformuleerd, die aan de hand van twee voorbeelden, de grondstoffen formaldehyde en nitrillen, nader werden uitgewerkt. Allereerst werd er een literatuuronderzoek uitgevoerd om de benodigde juridische, toxicologische en proces- en milieu-technologische informatie te vergaren. Daarbij is vastgesteld dat in bepaalde situaties grondstoffen kunnen worden geregistreerd als een "transported isolated intermediate". Van de chemische processen op de site Herkenbosch van Akzo Nobel Functional Chemicals B.V. zijn er vervolgens enkele geanalyseerd op de mogelijkheden en onmogelijkheden om via de variant van de "transported isolated intermediate" te kunnen voldoen aan de wettelijke verplichtingen zoals opgenomen in REACH. Daarbij werden de proces-omstandigheden en de mogelijk daaruit voort-vloeiende blootstellingen van de betrokken medewerkers aan genoemde grondstoffen vastgesteld. Vervolgens werden de onzekerheden in de gekozen werkwijze en in de gevonden resultaten nader bestudeerd en bediscussieerd onder andere aan de hand van de REACH regelgeving en aan de hand van enkele recente artikelen uit de open literatuur.
Alle resultaten zijn tenslotte op hun merites beoordeeld, bediscussieerd en correct bevonden.

Conclusies
Bij de registratie van een grondstof, waarvan de toepassing voldoet aan bepaalde kwalificaties, als een "transported isolated intermediate", mag een registrant bij de registratie van die toepassing volstaan met het verstrekken van verminderde informatie conform REACH artikel 18 (2) indien deze registrant bevestigt of verklaart dat hij de bevestiging heeft ontvangen van zowel de fabrikant/ importeur als de gebruiker (in of buiten de EU), dat de stof wordt vervaardigd en gebruikt onder “strikt gecontrolleerde omstandigheden” (“strictly controlled conditions”, SCC's), zoals beschreven in REACH artikel 18 (4). Zowel de registrant als de gebruiker zijn elk verantwoordelijk voor hun eigen verklaring over de SCC's. In dit onderzoeksproject is aangetoond dat deze benadering kan worden toegepast op de grondstoffen formaldehyde en nitrillen, zoals deze worden gebruikt in de vestiging Herkenbosch van AKZO Nobel Functional Chemicals B.V.. Zo kan tevens worden voldaan aan de verplichtingen van zowel een registrant als een downstream-gebruiker en kunnen hun onderlinge activiteiten en communicatie in het kader van REACH op een efficiënte, effectieve en eenduidige manier worden uitgevoerd.

Voordelen
De genoemde aanpak

- *voldoet volledig* aan REACH [zie art. 18 (2) en 18 (4)] en aan andere wetgeving.
- is van kracht *voor alle stoffen* op voorwaarde dat aan de verplichtingen van REACH art. 18 (2) en 18 (4) volledig is voldaan, zodat deze ook kan worden toegepast voor "substances of very high concern " zoals CRM's, PBT's en vPvB's.
- is zo *efficiënt en effectief* mogelijk voor de betreffende toepassing en is bovendien *eenduidig*.
- is *goed uitvoerbaar* en *sluit aan op andere verplichtingen* op het gebied van HSE en RA.
- vraagt *relatief weinig inspanningen* van zowel de registrant en de downstreamgebruiker als de autoriteiten *en leidt tot relatief lage kosten*.
- Het bovenstaande betekent dat ANFCH, gegeven de situatie en de dagelijkse praktijk op de site Herkenbosch, met succes deze methode toe zou kunnen passen voor veel van haar grondstoffen.
  Naar analogie hiermee geldt hetzelfde voor een belangrijk deel van de grondstoffen van een aanzienlijk deel van de chemische industrie.
  Echter, iedere keer opnieuw zal er voor een grondstof aangetoond dienen te worden dat deze “substance” is geproduceerd en wordt gebruikt onder “strictly controlled conditions” (SCC’s), zoals deze worden beschreven in REACH Artikel 18 (4),

1. THE GRADUATE SUBJECT

1.1 Introduction

Chemicals are an essential element in our society. They are incorporated into many products such as toys, medicines, clothing, detergents, etc. and play a very important role in the economy. Unsafe use of chemicals involves risks for humans and the environment.

It is of great importance to reduce the risks of (the use of) chemicals. Risk reduction deals with substances, preparations and substances in articles. For this there are established international rules. REACH is the new European regulation on chemical substances.
REACH is a acronym for: **R**egistration, **E**valuation, **A**uthorization and Restriction of **Ch**emicals.
In principle it applies to all chemicals: not only chemicals used in industrial processes but also in our day-to-day life, e.g. in cleaning products, paints and in articles intended for consumer use such as clothes, furniture and electrical appliances. It concerns all companies that deal with chemicals. REACH is therefore exceedingly relevant to all chemical industries.

The aim of REACH is that all companies in the supply chain of a chemical substance – from manufacturer, importer and distributor to customer - make sure that the production, marketing and use of substances will take place in a way as safe as possible. Companies are responsible for this. This means that REACH is important for everyone.

1.2 Overview of the thesis

In *this chapter* the reader will find a short introduction and an overview of this thesis.
Chapter 2 gives an impression on the background of this graduate subject both from a historical and from a practical point of view. The background of the research questions regarding this graduate subject is also explained and the research questions themselves (see paragraph 2.2) are formulated.

Akzo Nobel and the Dissolvine®Chelates are described in *Chapter 3* and some specific aspects in *Appendix 7.* The Dissolvine®Chelates are very useful products, despite the fact that they are produced with raw materials [see Appendix 1 & 5], which may pose a risk as appears e.g. from the classification of these substances according to Directive 67/548/EEC.

REACH, the new EU legislative framework for chemical substances, is outlined in *Chapter 4*, including the obligations for the industry in common and those with regard to the Registration and the compiling of the Chemical Safety Report and the development of Exposure Scenarios in particular.

In order to answer the research questions, as will be formulated in paragraph 2.2 and to investigate how to fulfill the duties of both an importer and a downstream user and their mutual activities regarding to REACH, as well as the duties of a responsible employer, two examples will be elaborated. In *Chapter 5* this will be done for the first example by means of the description and explanation of the exposure during the application of formaldehyde. For the second example, exposure during the application of nitriles, this will be done in *Chapter 6*. The research questions are fully discussed and answered in these chapters.

In *Chapter 7,* some points of attention and boundary conditions are outlined, regarding the results of chapter 5 & 6.

Uncertainty in a risk assessment in general and in case of REACH in particular, will be discussed in *Chapter 8* as well as two relevant examples of the recent literature regarding some uncertainties in the risk assessment and in case of REACH.

In *Chapter 9* the reader can take cognizance of the conclusions with regard to this graduate subject.

Finally, *Chapter 10* consists of the references and in the *appendices* some interesting aspects of REACH and (the raw materials needed for) the industrial synthesis of EDTA, both the Singer and the Strecker synthesis, are outlined. Also some specific aspects of the Dissolvine®Chelates are described:

Appendix 1: INDUSTRIAL SYNTHESIS OF EDTA
Appendix 2: PROCESSCHEME REACH & ISOLATED INTERMEDIATES
Appendix 3: INTERMEDIATES
Appendix 4: PROCESSCHEME CHEMICAL RISK ASSESSMENT UNDER REACH
Appendix 5: DANGEROUS CHEMICALS AT THE SITE ANFCH
Appendix 6: MEASUREMENTS IN CASE OF AN EMERGENCY
Appendix 7: SOME USEFUL AND ENVIRONMENTAL ASPECTS OF THE DISSOLVINE®CHELATES

2. BACKGROUND OF THE GRADUATE SUBJECT

2.1 History of the former and the new EU legislative framework for chemical substances

The former EU legislative framework for chemical substances was a patchwork of different Directives and Regulations which had developed historically. Introduced under regulation (EC) 793/93, the distinction between "existing" and "new" chemicals including different rules was based on the cut-off date of 1981. Chemicals being on the European Community market between 1 January 1971 and 18 September 1981 [listed in the **E**uropean **In**ventory of **E**xisting Commercial **C**hemical **S**ubstances (EINECS)] were called "existing" chemicals. In 1981, they numbered more than 100.000 different substances. Chemicals introduced to the market after 1981 [more than 3800, listed in the **E**uropean **LI**st of **N**otified **C**hemical **S**ubstances (ELINCS)] had been termed "new" chemicals.
While “new” chemicals had to be tested before they were placed on the market, there were no such provisions for "existing" chemicals. Thus, although some information existed on the properties and uses of existing substances, there was generally a lack of sufficient information publicly available in order to assess and control these substances effectively.

The former allocation of responsibilities was also not appropriate. Public authorities were responsible for undertaking risk assessments of substances rather than the enterprises that manufacture, import or use the substances. And these risk assessments were required to be comprehensive, rather than targeted and use-specific. Since 1993, only 141 high-volume chemicals had been identified as priority substances for risk assessment. Recommendations for risk reduction were only available for a limited number of the chemicals for which the whole evaluation process under Regulation (EC) 793/93 had been completed. Furthermore, former legislation required the manufacturers and importers of chemicals to provide information, but did not impose similar obligations on downstream users (industrial users and formulators) unless the substance had to be classified and a safety data sheet had to be supplied with it further down the supply chain. Thus, information on uses of substances was difficult to obtain and information about the exposure arising from downstream uses was generally scarce.
On the other hand, new chemicals had to be notified and tested starting from volumes as low as 10 kg. per year. This had been a barrier to innovation within the EU chemicals industry by discouraging research and invention of new substances and favouring the development and use of existing chemicals over new ones, causing the EU chemical industry to fall behind on its counterparts in the US and Japan.

The identification and assessment of risks - covering the possible hazards of a substance as well as exposure of humans and the environment to it – had proved to be slow, as had been the subsequent introduction of risk management measures. This system had not produced sufficient information about the effects of the majority of existing chemicals on human health and the environment.
It started in 1976 and restricted the marketing or use of only about 100 substances, including the use of some of them in articles, as well as the marketing to the general public of about 900 substances classified as carcinogenic, toxic to reproduction or mutagenic (CRM substances), published in 2001,

The 2 most important aims of the *new* chemical strategy are to improve protection of human health and the environment from the risks of chemicals while enhancing the competitiveness of the EU chemicals industry.

The Commissions Strategy for a Future Chemicals Policy (COM (2001) 88), outlined the result of a review of the former system and its new strategy for ensuring a high level of chemicals safety and a competitive chemicals industry through a system for **R**egistration, **E**valuation and **A**uthorisation of **Ch**emicals (**REACH**).
The 7 objectives that needed to be balanced within the overall framework of sustainable development were:

- Protection of human health and the environment
- Maintenance and enhancement of the competitiveness of the EU chemical industry
- Prevention of fragmentation of the internal market
- Increased transparency
- Integration with international efforts
- Promotion of non-animal testing
- Conformity with EU international obligations under the WTO.

Within the Council, the Heads of State gave the Competitiveness Council the responsibility for REACH. An ad hoc working group of representatives of the Competitiveness and Environment Ministries discussed the proposal in great detail during the period 2003 - 2006. The Economic and Social Committee adopted an opinion on REACH in April 2004 and adopted an additional opinion in July 2005.

The Proposal was communicated to the European Parliament and the Council in November 2003. During the first reading, work in the Parliament was led by the Committee on the Environment, Public Health & Food Safety, which co-operated for this purpose with the Committee for Internal Market and Consumer Protection and the Committee for Industry, Research and Energy.
Apart from these three committees, seven other parliamentary committees tabled amendments.
The European Parliament adopted its first reading opinion in its plenary session on 17 November 2005.
Following the Parliament's opinion, the Council reached a political agreement on a Common Position in the Competitiveness Council of 13 December 2005 under the UK Presidency.
The formal Common Position of the Council was approved on 27 June 2006. In July 2006 this position was formally submitted to the European Parliament, which intends to formally accept it in the first plenary session of September, hereby formally starting the second reading of the proposal.
The Commission adopted a Communication on the Common Position on 12 July 2006 and expressed its full support for the Common Position and in the balance found in the areas of registration and authorization. The Parliament adopted its second reading opinion on 13 December 2006.
The Council had adopted the Regulation on 18 December 2006 and REACH, described in chapter 4, went into effect on 1 June 2007.

2.2 Research questions in this graduate subject

The Dissolvine® chelates, produced by AkzoNobel and introduced more in detail in chapter 3, are very useful products which improve the performance of a variety of products and processes significantly. However, they are produced with the use of raw materials, which may pose a risk as appears e.g. from the classification of these substances according to Directive 67/548/EEC [see Appendix 5]. Without the use of these raw materials the Dissolvine® chelates couldn't be produced [see Appendix 1]. It is of utmost importance for ANFCH, as being both an importer and a downstream user and even more a responsible employer, to know what the consequences will be, concerning REACH for these raw materials.

According to REACH, raw materials may sometimes be considered as "transported isolated intermediates". In that case, a registrant can provide reduced registration information according to Article 18 (2), if he states or confirms that he has received confirmation from both the manufacturer/ importer and the user, that the substance is manufactured and used under "strictly controlled conditions" as described under Article 18 (4). Terms as 'transported isolated intermediates' and 'strictly controlled conditions' are explained in Appendix 3.

To assess if these raw materials could be considered as "transported isolated intermediates", it should be evaluated whether the conditions, as mentioned in Appendix 3, section 1, "On site isolated and transported isolated intermediates", are met.

If so it should be determined if these "transported isolated intermediates" are used under "strictly controlled conditions" during the production processes for EDTA and it should be evaluated if the following conditions, as detailed in REACH Article 18(4), are in place at the site of ANFCH:

(a) the substance is rigorously contained by technical means during its whole lifecycle including manufacture, purification, cleaning and maintenance of equipment, sampling, analysis, loading and unloading of equipment or vessels, waste disposal or purification and storage; (Appendix 3, section 9. "*Rigorous containment of the substance*")
(b) procedural and control technologies shall be used that minimise emission and any resulting exposure; (Appendix 3, section 10, "*Procedural and control technologies to minimise emission and any resulting exposure*")
(c) only properly trained and authorised personnel handle the substance; (Appendix 3, section 11, "*Handling of the substance by trained personnel*")
(d) in the case of cleaning and maintenance works, special procedures such as purging and washing are applied before the system is opened and entered;
(e) in cases of accident and when waste is generated, procedural and/or control technologies are used to minimise emissions and the resulting exposure during purification or cleaning and maintenance procedures; (Appendix 3, section 12, "*Cases of accident and when waste is generated*")
(f) substance-handling procedures are well documented and strictly supervised by the site operator.

Article 18(4) provides a wider definition of "strict control" than Article 17(3) which is limited to criteria (a) and (b) of the above list. This definition covers both: (i) normal operating conditions and (ii) non-routine operational circumstances such as maintenance and incidents.

Against this background the following research questions, regarding these very interesting and important aspects of REACH, could be formulated:

1. what is mentioned about the use of intermediates within REACH?
2. how can ANFCH be in compliance with these parts of REACH as efficiently and effectively as possible?
3. how can ANFCH prove that they will be in compliance with the REACH regulation regarding strictly controlled conditions in using intermediates ?
4. which uncertainties are important in estimating the risk of exposure to intermediates and how should ANFCH deal with these uncertainties?

These questions will be discussed in chapter 5 and 6 and answered in chapter 9. For that purpose and in order to investigate how to fulfill the duties of an importer and a downstream user regarding to REACH and their mutual activities, as well as the duties of a responsible employer, two examples will be elaborated. It is also important to find out how to act and to communicate as efficient and effective as possible in a univocal way. These two examples, which will be elaborated, in chapter 5 & 6 respectively, are:

1. formaldehyde (formaline 44 %), a raw material, used as reactant in the synthesis for Na_4EDTA.
2. nitriles, exclusively imported by ANFCH and used as a raw material in the synthesis of specific chelates.

In the first example the liquid substance is transported in tankers, unloaded in tanks and from these dosed into the process, where it reacts with the other raw materials, forming Na_4EDTA, a sequestrant agent. The second example will be elaborated for EDTN (Ethylenediaminetetraacetonitrile), a solid substance. It is packed in big bags, transported in containers, unloaded and stocked. Next, the solid product is dosed into a reactor filled with water forming a slurry, which is saponified with water and caustic soda to Na_4EDTA. More detailed information on both syntheses for Na_4EDTA and sequestrant agents is given in Appendix 1.

As title for this graduate subject is chosen:
SAFE USE OF CHEMICALS IN THE SUPPLY CHAIN
How to fulfill the duties of a legal entity, acting both as an importer and an industrial downstream user, regarding to raw materials as mentioned in REACH, as efficient and effective as possible in a unequivocal way.

The results of these investigations and the literature search will be reported and discussed in this thesis. On urgent request the results of this graduate subject should be considered as strictly confidential.

2.3 Research method

The study was conducted according to a roadmap and includes the topics mentioned below:

* BASIC ANALYSIS OF REACH LEGISLATION
  What is REACH? Why is it so important? And why for ANFCH? Which are the important legislative processes?
* OVERALL ANALYSIS OF THE PROCESSES AND THE END PRODUCTS WITHIN ANFCH, WITH A FOCUS ON REACH
  Which processes and end products are important with regard to REACH? Why? What does this mean for ANFCH?
* DETAILED ANALYSIS OF REACH LEGISLATION, WITH A FOCUS ON ANFCH
  What is the importance of REACH for the Dissolvine® chelates and for the raw materials of which they are produced? What requirements does ANFCH have to fulfil regarding REACH? What does a Chemical Safety Assessment mean? What is the REACH Exposure Scenario Concept? What are relevant, interesting research questions for this thesis?
* MAKING A CHOISE OF 2 SUITABLE AND REPRESENTATIVE PILOT RAW MATERIALS OUT OF A NUMBER OF ± 150
  Which raw materials are important, interesting, suitable and *representative with regard to REACH?*
* OVERALL STUDY OF LITERATURE
  What is mentioned in literature about REACH in general and about some interesting aspects of REACH for ANFCH, as mentioned in paragraph 2.2, and for this thesis in particular?
* DETAILED ANALYSIS OF PROCESSES WITHIN ANFCH, WITH A FOCUS ON 2 RAW MATERIALS AND REACH
  What is mentioned in literature about these raw materials regarding to REACH? What are their phisico-chemical, toxicological and ecotoxicological properties and what do these mean regarding to REACH ? Which uncertainties will be met by ANFCH? What do these mean regarding to REACH ?
* ASSESSING THE NEED OF EXECUTING MEASUREMENTS IN ORDER TO DETERMINE EXPOSURE TO SUBSTANCES
  What is the best way to determine exposure to substances and what is the best way to measure this?
* EXECUTING MEASUREMENTS UNDER REPRESENTATIVE CIRCUMSTANCES AND ANALYSIS OF THE RESULTS
  How can the measurements be executed under representative circumstances? What do the measurements tell us about the exposure and what does this mean for the employees and for ANFCH in common and with regard to REACH in particular? Which uncertainties have been met by ANFCH? What do these mean regarding to REACH ?
* DETAILED STUDY OF LITERATURE
  What is mentioned in literature about the above mentioned with regard to REACH?
* DISCUSSIONS, DRAWING CONCLUSIONS AND REPORTING THE RESULTS
  What conclusions can be drawn and what is the importance of these conclusions? Which uncertainties have been met by ANFCH? How to deal with these uncertainties? What is the best way to report and explain the results?

3 AKZO NOBEL & DISSOLVINE®CHELATES

3.1 AKZO NOBEL

Akzo Nobel is a Fortune Global 500 company and is listed on the Euronext Amsterdam stock exchange. It is also included on the Dow Jones Sustainability Indexes and FTSE4Good Index. Based in the Netherlands, we are a multicultural organization serving customers throughout the world with coatings and chemicals. We employ around 62,000 people and conduct our activities in these two segments, with operating subsidiaries in more than 80 countries. For more information see: www.akzonobel.com.

3.2 DISSOLVINE®CHELATES

Dissolvine®is the Akzo Nobel brand name for products known as chelates, chemicals that control the reactivity of metal ions. The BU Functional Chemicals is the responsible legal entity for the chelates. Dissolvine®chelates are marketed through regional centers in the Netherlands, the USA and Singapore. The Dissolvine®chelate range is produced in in Lima, Ohio (USA), in Suzhou and Ningbo (China), in Kvarntorp (Sweden) and in Herkenbosch (the Netherlands) [*the latter will be abbreviated as ANFCH*].

Dissolvine®chelating agents combine amine and carboxylic acid chemistry in one molecule. This chemical combination yields aminopolycarboxylates (APCs), which can form highly stable complexes with metal ions. Compared to other chelating agents, the Chelates are more stable over a wider range of temperatures and pH values, have a stronger affinity for metals and are significantly more efficient, cost effective and versatile. They have good water solubility and are inert to most chemicals.

As the word ‘chele’ implies (Greek for crab’s claw), chelates seize a metal ion and control it, making it very difficult for another substance to liberate it. Chelates form strong, water-soluble complexes that prevent undesirable precipitation, dissolve scale deposits and optimize oxidation processes. The Dissolvine®chelate product range includes chelating agents that bind and control metal ions, as well as metal chelates that introduce the right form of metal ions into a product or process.

For example, metal cations like calcium, magnesium and barium can form low water-soluble salts with carbonates, sulfates and phosphates that precipitate out of aqueous systems. These precipitates form scales that are very difficult to remove and reduce the efficiency of boilers and processing equipment. When small amounts Dissolvine®chelating agents are added to these systems, they complex the metal ions into a water-soluble form and dissolve the scale deposit so that it is removed in the cleaning process. In virtually any industrial process which uses water, Dissolvine®chelates can add or remove metals in a controlled way. They improve the efficiency and cost effectiveness of chemical processes significantly.

3.3 DISSOLVINE®CHELATES and their applications

The following chelates are supplied: EDTA, DTPA, HEDTA, NTA, GLDA, PDTA, EDG and Glucoheptonate.

*** EDTA:**
The most widely used strong, cost effective and general purpose chelating agent.

*** DTPA:**
Recommended when a stronger chelating agent is needed, such as during peroxide bleaching of pulp. It remains more effective under oxidizing conditions. It is also especially suitable for descaling in oilfield applications.

*** HEDTA:**
A chelating agent with similar efficacy to EDTA. Particularly useful when high solubility is needed at low pH and for stabilizing iron ions at high pH.

*** NTA:**
A readily biodegradable chelating agent that is not as strong as EDTA but used widely in cleaning processes and detergent applications. It has a higher temperature stability.

*** GLDA:**
A readily biodegradable chelating agent, that can be used as alternative for NTA and EDTA, especially in cleaning applications. It has an very high solubility at high and low pH. The major part of the molecule originates from a natural sustainable source, MonoSodiumGlutaminate, a product of the fermentation of beetmolasses.

*** EDG:**
A readily biodegradable chelating agent, effective when a relatively weak chelating agent can be used.

*** PDTA:**
A chelating agent especially developed for the photo-finishing process. It is very effective in the bleaching of photographic films and paper, due to the favorable redox-potentials it imparts to iron.

*** GLUCOHEPTONATE:**
A biodegradable chelating agent based on a carbohydrate. It is weaker than the aminopolycarboxylates mentioned above. However, it exhibits an exceptional chelating ability for iron and other transition metal ions at high pH. As with GLDA, the major part of the molecule originates from a natural sustainable source, namely dextrose syrup.

The Dissolvine®chelates product line makes chelates available for many industrial processes. The primary applications are described below (see also: www.dissolvine.com and www.micronutrients.info).

*** Agriculture**

Metal chelates act as carriers for micronutrients, ensuring that plants get the trace elements they need. Products can be applied on or in the soil or can be sprayed onto plants. High-purity metal chelates are available to meet the demands of soil-less culture. Chelates are used to soften water in order to prevent or dissolve scale in drip irrigation.

*** Building & Construction**

Rapid setting of Portland cement and gypsum can be a problem. In gypsum board mills the proper balance of multiple admixtures is essential for optimal operation. Dissolvine®chelates are applied as synthetic retarding agents.

*** Cleaning and detergents**

Dissolvine®chelates deactivate the heavy metal ions that are often introduced through raw materials in the manufacture of soap and of detergents that contain peroxides like hydrogenperoxide, percarbonates and perborates. They boost the effectiveness of biocides, can be used efficiently to soften water and act as (co-)builder in detergents.

*** Industrial Cleaning**

Metal salts can cause scaling problems in boilers, heat exchangers and other water circulation systems found in the power, brewing, sugar and dairy industries. Chelating agents form stable, water-soluble metal complexes with harmful metal ions, dissolving scale formations and preventing new scales from forming.

*** Feed additives**

Trace metal elements are important for the health and growth of animals. According to US law, Na_2H_2EDTA (Dissolvine®NA2-P) can be used to solubilize trace minerals in aqueous solutions, which are then added to animal feeds (US: 21CFR, sec 573.360). Dissolvine®chelates are also used as preservatives in animal feed.

*** Food fortification**

Iron is an essential element for good health. Ferrazone®, a foodgrade iron chelate, is a highly effective iron source in food fortification to combat iron deficiency anemia. In 2006, the US Food and Drug Administration (FDA) agreed with the self-affirmed GRAS (Generally Recognized as Safe) status of Ferrazone®.
In a number of countries Ferrazone® has been approved as an iron fortificant as well.
See also: www.Ferrazone.com.

*** Food preservation**

Heavy metal ions can catalyze the degradation of vegetable oils and fats that can make food and beverages rancid. Dissolvine®chelates (E-CA-10 and NA2-P) deactivate undesirable metal ions, preserving the quality of the food and increasing shelf life. Dissolvine®E-CA-10 is produced in compliance with HACCP regulations.

*** Gas sweetening**

In commercially available processes, ferric ions oxidize H_2S to elemental sulfur. Dissolvine®chelating agents activate the ferric ions and prevent them from precipitating. In DeNOx processes Dissolvine®metal chelates enable nitrous oxide to dissolve in water, making it available for chemical and bacterial reduction to nitrogen.

*** Metal plating and electronics**

Solutions containing copper ions are used in the production of printed circuit boards. Copper and nickel are used in plating of automotive parts. Chelates fulfill several functions: as a metal carrier and as a stabilizer of process baths.

*** Oil industry**

Dissolvine®chelating agents are widely used in various oilfield applications such as stimulation, completion, cementing and enhanced oil recovery to re-dissolve scales such as $SrSO_4$, $BaSO_4$ and $CaCO_3$.
Furthermore, they can prevent iron precipitation during acidizing and fracturing processes.

*** Personal care**

Heavy metal ions can catalyze the degradation of ingredients used in personal care products.
Dissolvine® chelating agents deactivate the undesirable metal ions, maintaining quality and improving shelf life.

*** Pharma**

Some of our products are qualified for use in the production of pharmaceuticals.

*** Photography**

Chelated ferric ions are used to oxidize metallic silver into soluble silver ions, which can then be washed from films. Dissolvine®chelating agents act as carriers of these ferric ions and play an essential role in accelerating and fine-tuning the reactivity of these ferric ions with metallic silver.

*** Polymer production**

Ferric (Fe^{3+}) and ferrous (Fe^{2+}) ions play a key role in initiating emulsion polymerization processes to produce Styrene-butadiene rubber (SBR) and Acrylonitrile-butadiene-styrene (ABS). Chelates act as carriers of ferric ions. They also conserve natural rubber lattices by deactivating metal ion impurities that can catalyze decomposition.

*** Printing ink**

Metal ions can cause the formation of insoluble resin soaps in water thinned inks.
For example, in offset printing, the formation of polyvalent metal soaps may cause unwanted discoloration.
Dissolvine®chelating agents are used to overcome these problems, resulting in clear and color-stable inks.

*** Pulp and paper**

Metal ions catalyze the decomposition of bleaching agents (e.g. peroxide, ozone and hydrosulfite) and can lead to brightness reversion of pulp and paper. Dissolvine®chelating agents are used to remove and deactivate metal ions.

*** Textiles**

During the scouring and bleaching of textile fibers, Dissolvine®chelating agents remove and deactivate metal ions that would otherwise catalyze the decomposition of the peroxide bleaching agent. They also improve the performance of dye baths, where metal ions like Ca and Mg inhibit dye penetrating the fiber.

3.4 DISSOLVINE®CHELATES and the environment

The convenience and economic advantages of using Dissolvine®chelates are coupled with their mild environmental profile. Dissolvine®chelates have been used for many years and extensively studied. Almost all of them have a very low toxicity to plants, animals and humans.
Several of the Dissolvine®chelates are readily biodegradable, as measured in the Closed Bottle Test (**OECD 301D**). with the remaining being inherently biodegradable. Additionally 2 of these products are mainly based on natural and sustainable resources, namely Glucoheptonaat and GLDA.
The biodegradation of the slower degrading ones can be accelerated when biotreated under slightly alkaline conditions. It has also been found that the metal complexes formed in natural environment are degraded photo-chemically. As with all chemicals, chelating agents should always be used responsibly, meeting the technical needs of the application without unnecessarily affecting the environment.

AkzoNobel actively participates in the Responsible Care® program of the Chemical Industry. Product Stewardship is an important component of this program, designed to minimize the environmental impact of chemical products throughout their lifecycle, including the impact of end-use applications.
Product Stewardship principles are fully integrated into the main business activities, such as development, manufacturing, transportation, and handling. AkzoNobel also closely liaise with her customers, evaluating the use of her products in their processes as well as handling their disposal.

With our strong global presence, AkzoNobel is fully aware of intricacies of national environmental legislation. We are thus able to be proactive in ensuring that our products meet or exceed legal requirements.
AkzoNobel plays a major role in the High Production Volume (HPV) chemicals testing programs, which are designed to make comprehensive product data available to regulatory authorities as well as to the public.
AkzoNobel is actively involved in the Risk Assessment on EDTA and NTA initiated by the European Community under council regulation 793/93, one thing and another together with other leading chemical producers.

AkzoNobel has carried out breakthrough research on the biodegradability of EDTA.
Evidence from various studies supports the classification of EDTA as inherently biodegradable, in line with OECD criteria [*Organization for Economic Cooperation & Development*].
Working closely with customers -who allowed us to test EDTA in their industrial wastewater treatment plants- we have developed a method that increase biodegredation under mild alkaline conditions. AkzoNobel has patented this technology, which is now available to our customers.

All Akzo Nobel sites have operational environmental management systems. Within Akzo Nobel, quality is a central concept. This is embodied in a program of structured activities for managing total quality.
Production sites in the Netherlands, the USA and Sweden are certified according to ISO 9001 and ISO 14001, with the production site in China pending.
ISO certification is only one aspect of our quality program. As a leading global supplier, Akzo Nobel is also committed to a process of continuous improvement in every aspect of its operations.

More details regarding some of the very useful properties of the Dissolvine® chelates and their environmental profile, including a lot of literature references, can be found in Appendix 7.

4. REACH, THE NEW EU LEGISLATIVE FRAMEWORK FOR CHEMICAL SUBSTANCES

4.1 REACH in general

REACH is the new EU legislative framework for chemical substances**.** It went into effect on 1st June 2007 to streamline and improve the former legislative framework on chemicals of the European Union (EU).
REACH requires that the industry has certain knowledge of the properties of its substances and manages potential risks.
Authorities should focus their resources on ensuring industry are meeting their obligations and taking action on substances of very high concern or where there is a need for Community action.
So REACH places greater responsibility on the industry to manage the risks that chemicals may pose to the health and the environment.
In principle REACH applies to all chemicals: not only chemicals used in industrial processes but also in our day-to-day life, for example in cleaning products, paints and in articles intended for consumer use such as clothes, furniture and electrical appliances.
The aims of REACH are to:

- Improve the protection of human health and the environment from the risks that can be caused by chemicals
- Enhance the competitiveness of the EU chemicals industry, a key sector for the EU economy.
- Promote alternative methods for the assessment of hazards of substances
- Ensure the free circulation of substances on the internal market of the European Union

REACH is a acronym for **R**egistration, **E**valuation, **A**uthorisation and Restriction of **Ch**emicals.

Registration requires producers and importers to obtain relevant information on chemical substances produced in or imported to the EU market in quantities greater than 1 tonne per year. It involves submitting a technical dossier containing information on the substance and information on how to effectively manage the risk entailed by using it. Quantities above 10 tonnes per year additionally require the submission of a Chemical Safety Report (CSR) to document the safety assessment of the substance.

Evaluation allows the regulatory authorities to decide on proposals for further testing and assess whether information provided by industry complies with the requirements (dossier evaluation). For selected substances, for which a risk to health or the environment is suspected, substance evaluation provides a mechanism to require industry to obtain more information.
Evaluation may also lead to the conclusion that action should be taken under the restrictions or authorisation procedures.

Authorisation may be required for substances of very high concern (carcinogens, mutagens, substances toxic to the reproductive system, and substances which are persistent, bio-accumulative and toxic, very persistent and very bio-accumulative or of equivalent concern).

Restrictions are the safety net of the system. Any substance on its own, in a preparation or in an article may be subject to Community-wide restrictions if its use poses unacceptable risks to health or the environment. Restrictions can be decided either for the use of a substance in certain products, the use by consumers or even for all uses (complete ban of a substance).

The former EU legislative framework for chemical substances was a patchwork of many different Directives and Regulations which has developed historically. There were different rules for “existing” and “new” chemicals. However, this system has not produced sufficient information about the effects of the majority of existing chemicals on human health and the environment.

The identification and assessment of risks - covering the possible hazards of a substance as well as exposure of humans and the environment to it – have proved to be slow, as have been the subsequent introduction of risk management measures.

The former chemical legislation, which distinguishes between so-called "existing" and "new" chemicals, is based on the cut-off date of 1981.

All chemicals that were put on the market before 1981 were called "*existing*" chemicals. In 1981, they numbered 100.106.
Chemicals introduced after 1981 (over 4300) were termed "*new*" chemicals.
While new chemicals had to be tested, there were no such provisions for the existing substances. Consequently, there is a general lack of knowledge on properties and uses of "existing" substances and the risk assessment process was slow, cumbersome and resource-intensive. For example, since 1993, only 140 high-volume chemicals (above 1000 tonnes) have been singled out as a priority for risk assessment and final reports are available for about 70 of these substances. These shortcomings have potentially put human health and the environment at risk. As regards new substances, the current system has also hampered research and innovation. New chemicals manufactured in quantities as low as 10 kg. were subject to testing requirements, causing the EU chemicals industry to lag behind its counterparts in the US and Japan in this regard.

REACH will replace the 40 existing legal acts and create a single system for *all* chemical substances and require manufacturers and importers to gather comprehensive information on the properties of all substances produced or imported in quantities higher than 1 tonne per year and to submit the necessary information to demonstrate their safe use in a registration dossier to the European Chemicals Agency. Failure to register will mean the substance cannot be manufactured or imported into the EU market.

Currently about 30.000 substances are in the EU market in volumes above one tonne. REACH will also provide encouragement to develop new substances as a result of better incentives for research and development and less burdensome requirements for registration of new chemicals.

REACH places greater responsibility on the industry to manage the risk of chemicals and provide appropriate safety information to professional users and, as far as the most hazardous substances are concerned, also to consumers.

Which industries will get obligations?
Manufacturers and importers are obliged to register substances they produce or import in quantities over 1 tonne per year. The registration requirement applies to substances on their own, in preparations and in articles under special conditions (intentional release). Failure to register means that the substance cannot be manufactured, imported or used in the EU market.
Downstream users of chemicals must apply the risk management measures for dangerous substances identified on the supplier Safety Data Sheets. They have a right to make their use of a substance known to the manufacturer in order to make it an identified use and have it covered in their supplier's chemical safety assessment. In this case they have to provide sufficient information to allow the supplier to prepare an exposure scenario for the use. Alternatively they can conduct their own chemical safety assessment and report this use to the chemicals agency.

What types of obligations will they get?
Titles I and IV came into effect on 1st June 2007. Title I only covers some general items.
Title IV - *Information in the Supply Chain* - is different in that it requires new format SDS's to be available from 1st June 2007. The changes from the current format are that sections 2 and 3 change places and an e-mail address of the competent person responsible for the SDS has to be included in section 1.
The first [real] REACH obligation, pre-registration, has taken place from 1 June 2008 to 1 December 2008.
Following pre-registration, registration deadlines apply on 30 November 2010, 31 May 2013 and 1 May 2018, depending on the volume band or level of concern of the substance. Starting on 1 June 2008, new substances need to be registered before they are placed on the market.

Registration obligations apply to manufacturers and importers of chemicals who need to gather comprehensive information on the properties of the substance they produced or imported over one tonne per year. This information and evidence demonstrating the safe use of the substance need to be submitted in a registration dossier to the European Chemicals Agency.
If a substance has been identified for authorisation, companies may only manufacture, import or use the substance after the so-called "sunset date" if they have obtained an authorisation for a particular use.

Companies can apply for an authorisation until 18 months before the “sunset date”, providing all relevant documentation, including an analysis of substitutes and where safer alternative substances are available, substitution plans, and an indication of relevant Research and Development plans if appropriate.
Companies using substances subject to restrictions must respect the conditions of the restrictions.

How will authorisation work in practice?
Around 1500 substances of very high concern may become subject to authorisation, including:

- CRMs (substances that are carcinogenic, mutagenic or toxic to reproduction), cat. 1 & 2,
- PBTs (substances with persistent, bio-accumulative and toxic properties),
- vPvBs (substances that are very persistent, very bio-accumulative),
- Substances identified from scientific evidence as causing probable serious effects to human health and the environment equivalent to those of the other categories mentioned above, for example certain endocrine disrupting substances (substances disturbing the body's hormone system). These will be identified on a case by case basis.

The authorisation system is intended to ensure that such substances will be progressively replaced wherever they cause unacceptable risks for human health and the environment or where there are no other reasons that justify carrying on using them. In particular, there may be applications where exposure to human beings or the environment is very limited and where risks can be adequately controlled. In other cases, the use of such substances can create substantial socio-economic benefits that outweigh the risks associated with the use (e.g. ensuring safety of equipment for cases where there is no suitable alternative). For these uses, special rules for authorisation have been defined.

For certain substances that are carcinogenic, mutagenic or toxic to the reproductive system (CMR substances), an authorisation will be granted if the producer or importer can show that risks from the use in question can be adequately controlled. This means that scientists can agree on a "safe threshold" below which a substance does not create negative effects to the human body or the environment.
For other CMR substances and substances with persistent, bio-accumulative or toxic properties (PBT, vPvB substances), where adequate control is not possible, an authorisation will only be granted if no safer alternative exists and if the socio-economic benefits of the use of the substance outweigh the risks.

4.2 Legislative Process of REACH

Within REACH manufacturers and importers will need to obtain information on the substances they manufacture or import and use this information to assess the risks arising from the uses and to ensure that the risks which the substances may present are properly managed.
In the chemical safety assessment, all life-cycle stages are to be considered, to identify potential risks and derive relevant risk management measures to adequately control these.
The life-cycle of a substance means the time span from its manufacture to its disposal (*cradle to grave*).
Registration, as mentioned before, documents the performance of this duty and requires manufacturers and importers to submit:

- a **technical dossier**, for substances in quantities of 1 tonne or more, and
- a **chemical safety report**, for substances in quantities of 10 tonnes or more.

The **technical dossier** contains information on the properties, uses and on the classification of a substance as well as guidance on safe use.
The **chemical safety report** (CSR) for substances manufactured or imported in quantities starting at 10 tonnes, documents the hazards and classification of a substance and the assessment as to whether the substance is PBT or vPvB. The CSR also describes ***exposure scenarios*** for specific uses of substances that are classified as dangerous or are PBT or vPvB substances.

The **exposure scenarios** must include the appropriate risk management measures and operational conditions that, when properly implemented, ensure that the risks from the use(-s) of the substance are adequately controlled.

Exposure scenarios need to be developed to cover all “identified uses” which are the manufacturers’ or importers’ own uses, and uses which are made known to the manufacturer or importer by his downstream users and which the manufacturer or importer includes in his assessment.
Relevant exposure scenarios will need to be annexed to the safety data sheets that will be supplied to downstream users and distributors. So the “exposure scenario” is a ***core element*** within REACH.
The term Exposure Scenario is defined in REACH, Annex I as:

> “*An exposure scenario is the set of conditions that describe how the substance is manufactured or used during its life-cycle and how the manufacturer or importer controls, or recommends downstream users to control, exposures of humans and the environment*.”

So a Exposure Scenario defines the operational conditions of use and the accessory suitable risk management measures under which safe use is possible.
It is primarily the task of the manufacturers and importers of substances to develop exposure scenarios as part of their chemical safety report and the registration dossier.
Only in special cases does a downstream user have to develop an exposure scenario.
Registrants frequently do not know for what purpose and how a substance is used in the supply chain. They can therefore either make assumptions or collect information from their downstream users on the conditions of use. The latter approach ensures that the actual situation is better reflected in the chemical safety assessment and thus the exposure scenarios are likely to cover the majority of conditions of use at downstream user level.
Since the registrant is obliged to define exposure scenarios for each life cycle stage, it is a major challenge for him to collect the information on use and exposure needed.
However, industrial users of chemical products also have an interest to support manufacturers and importers in registering substances for their uses. This is to avoid sourcing problems or inappropriate risk management advice that could occur if the supplier fails to correctly register the substance.
Next to it, it is the obligation of each user of a substance to make sure that his specific use has been included in the exposure scenario. He has to compare the conditions described and the risk management measures recommended in the exposure scenarios with those in his own process. If there is no accordance he has to change his own process or this specific use has yet to be registrated.

The increased emphasis on the Chemical Safety Assessment and the communication regarding safe use of chemicals in the supply chain requires a major build-up of competence throughout industry.

4.3 The REACH Exposure Scenario Concept

Under REACH, the Exposure Scenario (ES) describes the conditions under which a substance (as such, in a preparation or in an article) or a group of substances can be safely used. In doing so, scenarios should also be used to make an inventory of possible releases and to identify needs for risk mitigation.

- The ES is an element in the Chemical Safety Assessment (CSA) based on which the exposure assessment and the risk characterisation is carried out.
- An ES covers the entire life-cycle of a dangerous substance
- A dangerous substance/preparation can have different uses and can therefore have several, different ES’s.
- An ES describes the safe use of a substance, taking account of the various types of risks for humans and the environment
- An ES consists of a name (short title) and information on the operational conditions of use and the risk management measures that ensure adequate control of risks.
- The ES is an instrument for communicating operational conditions of use and risk [ES integrated into the Safety Data Sheet (SDS) system].
- The word ‘exposure’ is the scientific term for ‘coming into contact with something’: any type of contact between a person or the environment and a substance is an exposure.
- The exposure can take different routes, as humans take up and the environment receives substances through various channels, which are called exposure routes or exposure pathways.
- The exposure level of humans or the environment – the concentration or dose they are exposed to - is a numeric value that relates to the specific exposure route through which the substance is taken up. The (severity of the) effect will depend, in addition to the exposure level, on the duration and frequency with which the exposure occurs.
- The exposure level can, together with its duration and frequency, be determined by estimation or measurement. Under REACH, exposure estimations – or measurements of exposure levels- are performed in the frame of a chemical safety assessment.

The exposure scenario (ES) describes the 'conditions of use', which determine the exposure level. The conditions of use are divided into two types of parameters: the *operational conditions of use* and the *risk management measures*.
The *operational conditions of use* (e.g. amount, application, temperature, duration and frequency of use) describe how a process or activity is carried out. In principle, the operational conditions of use determine the emission of a substance from a process.
Risk Management Measures (e.g. local exhaust ventilation, filters, sewage treatment plants or personal protective equipment [gloves, respirators and goggles]) include all measures and devices that are applied to prevent substance which is emitted from a certain process from reaching humans or the environment.
The inherent properties of the substance (e.g. volatility, water solubility) and the local conditions (e.g. river water flow, specifics of the work area) determine the level of emission to and concentration in a certain environmental compartment and exposure to certain target groups, like consumers and workers.
Other parameters could relate to the operating temperature, pressures, or pH as well as the degree of containment of technical equipment (e.g. is the substance handled in a enclosed vessel or applied outside).
Information about the surroundings of the place where the chemical is used, can also be part of the ES. Information may be needed, for example, on the dilution of the substance in surface water or the air volume of the workplace to which a substance is emitted.
Once a registrant has identified the relevant uses of his substance in the market and the broad conditions of use, he can derive a tentative exposure scenario and based on this assess the exposure and risk. Depending on the result one or more iterations of exposure estimation and risk characterisation may be carried out before the final ES can be defined.
The emission estimation, exposure assessment and risk characterisation is needed to decide whether the conditions described in the ES ensure safe handling.

4.4 Approach scheme for Exposure Scenarios within REACH

In chapter 4.2, a number of general principles for Exposure Scenarios [ESs] are described.
In this chapter a detailed description of work processes will given that may be conducted for identification of uses, for assessment of exposure of and risks to workers, the environment and consumers and by that developing the final Exposure Scenario.
This work process may proceed in the following 6 consecutive steps:

IDENTIFICATION OF USES AND USE PROCESSES

Exposure Scenario s shall be developed for manufacturing processes and for identified uses of the substance on its own or in a preparation (cf. annex 1 of REACH). While a manufacturer or importer registering a chemical will have information on his own manufacturing process(es) and use(s) of the chemical, information on uses further down the chemical supply chain may be more sparse.
REACH requires that ESs shall be developed for identified uses, and provides any downstream user with the possibility to make a use known to his supplier with the purpose of making his use an "identified use" for which an ES shall be developed to the extent that the supplier accepts and supports this use. However, a manufacturer or importer is not obliged to be proactive in seeking information on uses of his chemicals, but he can await a reaction from his customers before developing an ES for uses that were not previously identified.
If a downstream user makes his use known to his supplier, the supplier may decide to develop an ES for that specific use and update his Chemical Safety Assessment.

DESCRIPTION OF MANUFACTURING OR USE PROCESS

Drafting a "tentative" ES for a manufacturing process or an identified use, it may be an advantage to develop a description of the manufacturing or use process that forms the basis for developing the ES.
A general identification of emission pathways at the different lifecycle steps needs to be considered in the description of the processes, i.e., manufacturing, formulation, industrial use, professional use, consumer use, service-life and the waste phase. A number of individual activities may be identified. The possible contribution of each of these activities to the overall exposure should be considered.

DEVELOPMENT OF A "TENTATIVE" EXPOSURE SCENARIO

It may be beneficial to set up a "tentative" ES for the process that forms the basis for conducting an exposure estimate and a risk characterisation with the purpose of assessing whether risks are well controlled. This "tentative" ES could either be developed by the manufacturer or importer or by the downstream user, or an already developed ES could be taken over and used directly or be modified. The tentative ES should contain the main determinants of exposure, but the level of detail depends on the available data. Sometimes, only minimal exposure information may be available while in other cases, an extensive data set on exposure conditions is available. The tentative ES can be used to explore if the available data will be sufficient to conclude on adequate control of risks or whether further detailing is necessary.

ASSESMENT OF EXPOSURE AND RISKS

The "tentative" Exposure Scenario defines the starting assumptions on the process, which in combination with information on the intrinsic (hazard) properties of the substance feed into the exposure estimation and risk characterisation parts of the Chemical Safety Assessment.
It would be useful if this could be done by use of available approaches or tools or standard phrases.
The "tentative" Exposure Scenario thus defines the set-up for the exposure estimate.
In the Chemical Safety Assessment process, exposure levels are quantified and compared with the appropriate Derived No-Effect-Level (DNEL) for the relevant human population or the Predicted No-Effect-Concentration (PNEC) for the relevant environmental compartment.
If, based on the tentative ES, it cannot be demonstrated in the Chemical Safety Assessment process that risks are adequately controlled, further work would be needed.
This could include revisions to the manufacture or use process and the description in the "tentative" Exposure Scenario (changes of process, operational condition, duration or frequency of activities, handling of waste, improved or added Risk Management Measures, etc.), but could also include generation of more precise hazard information and/or a more advanced precise exposure estimate.

DEFINING THE "FINAL" EXPOSURE SCENARIO

When it has been satisfactorily demonstrated through the development of a "tentative" ES and the subsequent exposure estimate and risk characterisation in the Chemical Safety Assessment process that under the specified operational conditions and Risk Management Measures (RMM's) risks are adequately controlled, information on those operational conditions and RMM's is extracted into the "final" ES. This "final" ES is valid only for the substance and the process that have been assessed.
However, it might also be applicable for other substances with similar or less severe properties, if they are used in the same way as described in the "final" ES provided the substance properties do not change the process conditions or the efficiency of RMM's significantly.
When an ES is developed for a preparation, the final ES will of course pertain to all substances in the preparation. This means that even though some substances in the preparation could be used without RMM's, the RMM's required for the substance of highest risk would be decisive.

DEVELOPING THE ANNEX TO THE SDS

The "final" Exposure Scenario or a summary consisting of relevant extracts of the "final" ES shall be supplied to downstream users as an annex to the SDS. A structured format for the ES should be used with standardised headings in order to improve the communication to the downstream users.
When more than one ES have been developed for a substance (e.g. due to different uses requiring significantly different RMM's) separate annexes are required.
If the supplier is aware of his customer's intended use, he may then provide the SDS and the specific annex with the ES for this use.
Alternatively, he may provide the SDS and all available annexes with ES's for all the identified uses. In the latter case, the downstream user must be able to identify the annex with the ES relevant for his use, which requires a sufficiently precise description of the use.
A standardised structure of an ES is proposed in REACH' Annex 1 section 5.1.1.
Although the structure may be the same for both the "final" ES as part of the Registration dossier and the annex to the SDS, the level of detail may be less in the annex.
However, the information given in the annex must be sufficient for a precise identification of the use process and which RMM's are required under which operational conditions.
Use of standard phrases could be considered for developing of multilingual ES tools.
The requirement that all information guiding on safe use for a specified use shall be compiled in the annex to the SDS, will probably lead to a repetition of some information, as some of the information contained in the ES on safe use is required in the main text of the SDS as well.

4.5 REACH and the Dissolvine®chelates

The Dissolvine®chelates, produced by AkzoNobel, are very useful products as shown in chapter 3. However, they are produced with the use raw materials, which may pose a risk as appears e.g. from the classification of these according to Directive 67/548/EEC [see Appendix 5].
Without the use of these raw materials the Dissolvine®chelates couldn't be produced. [see Appendix 1].
It is of utmost importance for ANFCH, as being both an importer and a downstream user and even more a responsible employer, to know what the consequences will be, concerning REACH for these raw materials and to find out how to act and to communicate as efficient and effective as possible in a unequivocal way.

Under specific circumstances, raw materials could be seen as intermediates as mentioned within REACH. In the following the matter of strictly controlled conditions in the use of intermediates (see Appendix 3) for the production of Dissolvine®chelates is discussed, the research questions [see paragraph 2.2] will be answered and an investigation will be made to establish how to fulfill the duties of both a downstream user and an importer and their mutual activities regarding to REACH as well as the duties of a responsible employer.
For those purposes, two examples will be elaborated in chapter 5 & 6 respectively. The first example is formaldehyde (44 wt% solution), the second EDTN (Ethylenediaminetetraacetonitrile).

5. EXPOSURE DURING THE APPLICATION OF FORMALDEHYDE BY ANFCH

5.1 General

Formaldehyde (as formalin, a 44 wt% solution in water) is used by ANFCH as reactant in the so called Strecker synthesis for Na_4EDTA, which is described in Appendix 1.
The end product is a 40 wt% solution of Na_4EDTA in water (DISSOLVINE E-39 or E-45).

5.2 Unloading and storage of formalin (44%)

Formalin is supplied in a tanker and unloaded with a hose and a stationary pump into a storage tank. During unloading an air mixture containing formaldehyde will disappear from the storage tank to an active-carbon filter, in which it will be stripped of formaldehyde and after that it will be emitted to the air. After unloading, the hose and the piping are rinsed with water which is discharged into the storage tank. The supply and storage of formalin is at elevated temperature to prevent para-formaldehyde formation. The scenario approach leads to the following moments of exposure. Where necessary risk mitigation will be outlined.

MOMENT OF EXPOSURE 5.2.1
There is an exposure to formaldehyde during uncoupling of the (rinsed) unloading hose of the tanker and during monitoring the unloading process. The work is done alternately by 1 of 3 unloading operators. About 2 tankers are unloaded per day, yearly approximately 520. Each unloading takes about 0.75 hours and will take place inside a restricted area.
Measurements (see § 5.4) show that the concentration, to which the operator is exposed, is between 0.02 and 0.05 mg/m^3 . The operator will use personal protective equipment during coupling and uncoupling (workwear, safety shoes and helmet, chemical resistant gloves, full face mask), but no compressed air.

MOMENT OF EXPOSURE 5.2.2
During unloading an air mixture containing formaldehyde will disappear for about 0.75 hours from the storage tank to the active carbon filter, in which it will be stripped. Measurements (see § 5.4) show that the emission of formaldehyde to air after passing through the active-carbon filter, is 0.02 - 0.05 mg/m^3.

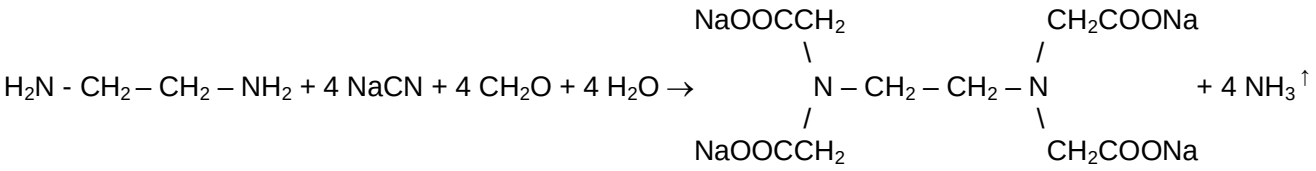
MOMENT OF EXPOSURE 5.2.3
If the active carbon is saturated, it is disposed as hazardous waste in an enclosed container.
All the work is proceeded according to established procedures, including the use of PPE (industrial clothing chemical-resistant gloves, safety shoes and helmet and gas mask). This is strictly monitored.
The exposure to formaldehyde during these activities is therefore virtually none.

MOMENT OF EXPOSURE 5.2.4
During maintenance of the unloading and storage equipment, operators and maintenance workers will work according to established procedures incorporated in Standard Operation Procedures (SOP). This includes e.g. Safe Work Permits [including thoroughly pre-rinsing the equipment and the use of PPE, and if necessary compressed air]. The exposure during these activities is therefore virtually nil.

MOMENT OF EXPOSURE 5.2.5
In case of an emergency the Site Emergency Plan will become effective and safety workers, equipped with sufficient and appropriate PPE's (if necessary also compressed air) will control the emergency

5.3 Application of formalin in the production process

Formalin (44 wt% formaldehyde in water) is pumped from the storage tank through a closed piping and dosed below the water level of a stirred closed reactor, in which the Strecker synthesis is performed. The process is controlled and monitored from the operator room, separated from the process area. This is done by operators using an automated process control system (DCS).
The Strecker synthesis is as follows:



N.B.: To illustrate the Strecker synthesis, ethylenediamine (EDA) was chosen as raw material but the comment applies to all primary and secondary amines. From ethylenediamine, sodium cyanide, formaldehyde and water the tetra sodium salt of ethylenediaminetetraaceticacid is formed, with liberation of the by-product ammonia.

The dosage of raw materials is such that, given the process temperature and the chemical properties of these substances, they react almost instantaneously when they get mixed. This is very important for the process and for the quality of the final products, so a minimum amount of by-products is formed.
A charge takes about 8 hours. Formalin is dosed during ca. 3 hours, each charge approx. 4000 kg.
The process temperature is 90 - 105 °C, depending on the stage of the process. Formaldehyde will only release as a result of leakage losses through flanges, through the (closed) manhole of the reactor etc..
At the end of each batch, samples are taken to check the quality of the product (an approximately 40 wt% solution in water). The reactor content is currently free of formaldehyde.
After finishing each batch the reactor content is pumped into one of the storage tanks for finished products and from there transported to "external downstream users" for their specific application(s) or to "internal downstream users" for use in one of the follow-up processes at the site.
In case of product exchange (another amine than EDA), the reactor, pump and piping are rinsed with water which is discharged into the storage tanks for finished products. The finished products will be delivered to clients either in bulk, or packed into 200-L plastic drums or 1000-L IBC's.
During a shift operators will stay 2 - 3 hours in the process area and 5 - 6 hours in the operator room.

MOMENT OF EXPOSURE 5.3.1
The process takes place in the liquid phase in a closed reactor. A charge lasts about 8 hours during which formalin is dosed during ca. 3 hours, per charge approximate 4000 kg. The temperature of the process fluid is 90 to 105 °C, depending on the stage of the process.
Through an enclosed piping system, raw materials are dosed into the reactor where they are kept under liguid level. They react almost instantaneously when they get mixed. So formaldehyde will only release as a result of leakage losses through flanges, through the (closed) manhole of the reactor etc..
During their 8-hours shift operators will stay and work 2 - 3 hours in the process area and 5 - 6 hours in the operator room. Measurements in the process area show that the formaldehyde concentration to which the operators are exposed, will be between 0.01 and 0.02 mg/m^3 .

MOMENT OF EXPOSURE 5.3.2
At the end of each batch, sampling will be performed by draining process liquid from the reactor from a sample loop. There is no formaldehyde in the process fluid (below detection limit).
So exposure of an operator to formaldehyde during sampling is virtually none.

MOMENT OF EXPOSURE 5.3.3
During maintenance of equipment, operators and maintenance workers will work according to established procedures incorporated in Standard Operation Procedures (SOP). This includes e.g. Safe Work Permits [including uncoupling, isolating and thoroughly pre-rinsing of the process equipment, the use of PPE and if necessary compressed air]. Exposure to formaldehyde during these activities is therefore virtually none.

MOMENT OF EXPOSURE 5.3.4
In case of an emergency the Site Emergency Plan will become effective and safety workers, well equipped with sufficient and suitable PPE's and if necessary also compressed air, will control the emergency.

MOMENT OF EXPOSURE 5.3.5
The final products DISSOLVINE E-39 or E-45 (respectively a 39 or 45 wt% solution of Na_4EDTA in water, in case of using EDA as raw material) are free of formaldehyde (below detection limit). Therefore, further downstream in the chain, there will be no exposures to formaldehyde, neither for further processing within ANFCH nor for downstream users of Na_4EDTA. These products as such have no consumer applications.

5.4 Additional issues related to exposure to formaldehyde

Measurements
Measurements of exposure to formaldehyde (as mentioned in § 5.2 and 5.3) have been executed by a certified consultant, under typical and representative circumstances for the jobs to be done.
Typical, because at the ANFCH site the formalin unloading area and the concerning process area are the only places where people could be exposed to formaldehyde originated from the own chemical processes.
Representative, because both the unloading of formalin and the Strecker synthesis have been executed in a normal way according to established procedures incorporated in Standard Operation Procedures (SOP).

Measurements [*with SEP-pack cartridges and using calibrated Gilian Gilair pumps, characterized by an extremely constant flow*] and analyses have both been executed according to NIOSH 2016 [2003].

Results have been evaluated according to NEN 689 ("*Leidraad voor de beoordeling van de bloot-stelling bij inademing van chemische stoffen voor de vergelijking met de grenswaarden en de meetstrategie", 1995*).
Based on literature data, the sum of the systematic error in sampling and measurement and the accidental error in sampling is no more than 10-20%.
So this is an accurate way to determine the exposure to formaldehyde of the workers concerned.

Assessment if formaldehye could be considered as a "transported isolated intermediate"
According to REACH [article 3 (15)] an *intermediate* is defined as

> "*a substance that is manufactured for and consumed in or used for chemical processing in order to be transformed into another substance(s)*"

Therefore intermediates should not be present in the final manufactured substance (except possibly as an impurity).

Under REACH different types of intermediates are defined:

- Non-isolated intermediates
- Isolated intermediates
    * On-site (non transported) isolated intermediates
    * Transported isolated intermediates

> **A non-isolated intermediate** is *an intermediate that during synthesis is not intentionally removed (except for sampling) from the equipment in which the synthesis takes place. Such equipment includes the reaction vessel, its ancillary equipment, and any equipment through which the substance(s) pass(es) during a continuous flow or batch process as well as the pipework for transfer from one vessel to another for the purpose of the next reaction step, but it excludes tanks or other vessels in which the substance(s) are stored after the manufacture* (*Article 3 (15)(a)*).
>
> **On-site isolated intermediate** means *an intermediate not meeting the criteria of a non-isolated intermediate and where the manufacture of the intermediate and the synthesis of (an)other substance(s) from that intermediate take place on the same site, operated by one or more legal entities (Article 3 (15)(b)).*
>
> **A site** means *a single location, in which, if there is more than one manufacturer of (a) substance(s), certain infrastructure and facilities are shared (Article 3(16)).*
>
> **A transported isolated intermediate** is *an intermediate not meeting the criteria of a non-isolated intermediate and transported between or supplied to other sites (Article 3 (15)(c)).*

It should be concluded that the substance formaldehyde (as formalin, a 44 wt% solution) as used by ANFCH as a raw material in the "Strecker" synthesis for Na_4EDTA, according to REACH may be seen as a "transported isolated intermediate".

Assessment if formaldehyde is used under "strictly controlled conditions"
It should be evaluated if the following conditions, as detailed in REACH Article 18(4), are in place at the site of ANFCH during the production processes for Na_4EDTA:

(a) the substance is rigorously contained by technical means during its whole lifecycle including manufacture, purification, cleaning and maintenance of equipment, sampling, analysis, loading and unloading of equipment or vessels, waste disposal or purification and storage; (*Appendix 3, section 9. "Rigorous containment of the substance"*)
(b) procedural and control technologies shall be used that minimise emission and any resulting exposure; (*Appendix 3, section 10, "Procedural and control technologies to minimise emission and any resulting exposure"*)
(c) only properly trained and authorised personnel handle the substance; (*Appendix 3, section 11, "Handling of the substance by trained personnel*")
(d) in the case of cleaning and maintenance works, special procedures such as purging and washing are applied before the system is opened and entered;
(e) in cases of accident and when waste is generated, procedural and/or control technologies are used to minimise emissions and the resulting exposure during purification or cleaning and maintenance procedures; (*Appendix 3, section 12, "Cases of accident and where waste is generated"*)
(f) substance-handling procedures are well documented and strictly supervised by the site operator.

These aspects will be evaluated in the next sub-paragraphs.

Identification of potential emissions to the workplace
Formalin is supplied in a tanker and unloaded with a hose and a stationary pump into a storage tank. After unloading, the hose and the piping are rinsed with water which is discharged into the storage tank. The supply and storage of formalin is at elevated temperature to prevent para-formaldehyde formation.
There is an exposure to formaldehyde during uncoupling of the (rinsed) unloading hose of the tanker and during monitoring the unloading process [vapour from the storage tank cleaned in an active carbon filter].

The unloading process is controlled and monitored by an operator; he will do this partly from a distance. The work is done alternately by 1 of 3 unloading operators.
About 2 tankers are unloaded per day, yearly about 520. Each unloading takes about 0.75 hours and will take place inside a restricted area. Measurements show that the concentration, to which the operator is exposed, is between 0.02 and 0.05 mg/m^3.
During coupling and uncoupling, the operator will use personal protective equipment (workwear, safety shoes and helmet, chemical resistant gloves, full face mask), but no compressed air.

Formaldehyde (as formalin, a 44 wt% solution in water) is used by ANFCH as a raw material in the "Strecker" synthesis for Na_4EDTA. The process takes place in the liquid phase in a closed reactor. Measurements in the process area, where the reactors are established, show that the formaldehyde concentration to which the operators are exposed will be between 0.01 and 0.02 mg/m^3.
During their 8-hours shift, the operators work 5 to 6 hours in the operator room and 2 to 3 hours in the process area, where they have to wear industrial clothing, safety shoes, safety glasses and a helmet.

At the end of each batch, sampling will be performed by draining process liquid from the reactor from a sample loop, using chemical resistant gloves. At this stage there is no formaldehyde in the processed fluid (below detection limit).
So exposure of an operator to formaldehyde during sampling is virtually none.

During maintenance of the process equipment, operators and maintenance workers, wearing industrial clothing, safety shoes, safety glasses and a helmet, will act according to established procedures part of Standard Operation Procedures (SOP) including e.g. Safe Work Permits. This includes uncoupling and isolating of the process equipment, thoroughly pre-rinsing the plants and the use of (additional) PPE, including compressed air if necessary.

In case of an emergency, the Site Emergency Plan will become effective and safety workers, well equipped with sufficient & appropriate PPE (and if necessary compressed air), will control the emergency.

The final products DISSOLVINE E-39 or E-45 (respectively a 39 or 45 wt% solution of Na_4EDTA in water (in case of using EDA as raw material) are free of formaldehyde (below detection limit). Therefore, further downstream in the chain, there will be no exposures to formaldehyde, neither for downstream users of Na_4EDTA nor for further processing within ANFCH. The products as such have no consumer applications.

Identification of potential emissions to the environment (air, wastewater, soil, etc.)
During unloading an air mixture containing formaldehyde will disappear for about 0.75 hours from the storage tank to an active-carbon filter, in which it will be stripped of formaldehyde and after that it will be emitted to the air. Measurements show that the emission of formaldehyde to air after passing through the active-carbon filter is between 0.02 and 0.05 mg/m^3, on yearly basis circa 0.8 gramme.

During storage, there is no exposure of the environment to formaldehyde. The tank is equipped with a pressure vacuum valve which enables air to stream towards the tank during dosing to the process.

Formaldehyde (as formalin, a 44 wt% solution in water) is used by ANFCH as a raw material in the "Strecker" synthesis for Na_4EDTA. The process takes place in the liquid phase in a closed reactor. Measurements in the process area, where the reactors are established, show that the formaldehyde concentration will be between 0.01 and 0.02 mg/m^3.
The process area is provided with a ventilation system which assures that the air within the process area, will be refreshed 4 times per hour, which results in an yearly emission to air of about 700 kg..

For accidental situations with formaldehyde in the context of the BRZO'99 (the dutch post Seveso legislation) a quantitative risk analysis (QRA) using the program Safety.NL has been prepared. This QRA shows that the “Individual Risk” [in dutch: plaatsgebonden risico (PR)], caused by the use of formalin in the situation as described for ANFCH, is mainly determined by the handling activities and in particular the risk of catastrophic failure of the unloading hose. This is a very important issue for the internal management in order to secure working under strictly controlled conditions. So this is part of the Standard Operation Procedures (SOP), regarding preventive maintenance.

Under normal operational circumstances, there will be no emissions of formaldehyde to the soil or waste water neither during storage nor during the production process, due to the transport and storage methods and equipment for formaldehyde and the application of enclosed systems and piping systems in the production process [made of appropriate materials (stainless steel) for these substances], combined with the specific production process, of which the control, recipe and monitoring is audited by operators using an automated process control system (DCS) while the operators are audited by the process computer.

Modelling estimations or available monitoring data during unloading en production
This is not considered to be necessary as exposure is very low compared to TWA.

Procedural and control technologies to minimize emission and resulting exposure
Formalin is supplied in a tanker and unloaded with a hose and a stationary pump into a storage tank. After unloading, the hose and the piping are rinsed with water which is discharged into the storage tank.
There is an exposure to formaldehyde during uncoupling of the (rinsed) unloading hose of the tanker and during monitoring the unloading process. The work is done alternately by 1 of 3 unloading operators.
About 2 tankers are unloaded per day, yearly approximately 520. An unloading takes about 0.75 hours.
Measurements show that the concentration, to which the operator is exposed, is between 0.02 and 0.05 mg/m^3. The unloading operator will use personal protective equipment during coupling and uncoupling (workwear, safety shoes and helmet, chemical resistant gloves, full face mask), but no compressed air.

During their 8-hours shift, the operators work 5 to 6 hours in the operator room and 2 to 3 hours in the process area, where they have to wear industrial clothing, safety shoes, safety glasses and a helmet.
Measurements in the process area, where the reactors are established, show that the formaldehyde concentration will be between 0.01 and 0.02 mg/m^3.

During loading and unloading, operation and maintenance of the process equipment, logistic personnel, operators and maintenance workers will work according to established procedures incorporated in Standard Operation Procedures (SOP) including e.g. Safe Work Permits. Operators and maintenance workers have to use PPE (personal protection equipment, including compressed air) if necessary.

The logistics and chemical processes are controlled and monitored from the operator room by operators using an automated process control system (DCS) and the operators are audited by the process computer.

Under normal operational circumstances, there will be no emissions of formaldehyde to the soil or waste water neither during storage nor during the production process, due to the transport and storage methods and equipment for formaldehyde and the application of enclosed systems and piping systems in the production process [made of appropriate materials (stainless steel) for these substances], combined with the specific production process, of which the control, recipe and monitoring is audited by operators using an automated process control system (DCS) while the operators are audited by the process computer.

In case of an emergency, the Site Emergency Plan will become effective and safety workers, well equipped with sufficient and appropriate PPE (and if necessary also compressed air), will control the emergency.

Handling of substance by trained and authorized personnel
All people working at the Herkenbosch site, including contractors, must be well educated, well trained and authorized for the jobs they are doing. The Human Resources Department will check this continuously.

During loading and unloading, operation and maintenance of the equipment, logistic personnel, operators and maintenance workers will work according to established procedures incorporated in Standard Operation Procedures (SOP) including e.g. Safe Work Permits. Operators and maintenance workers, wearing industrial clothing, safety shoes, safety glasses and a helmet, have to use additional personal protection equipment (PPE), including e.g. chemical resistant gloves, full face mask or compressed air if necessary.

The chemical processes are controlled and monitored from the operator room by operators using an automated process control system (DCS) and the operators are audited by the process computer.

In case of an emergency, the Site Emergency Plan will become effective and safety workers, well equipped with sufficient and appropriate PPE (and if necessary also compressed air), will control the emergency.

5.5 Conclusions related to the raw material formaldehyde

The conclusion, which can and should be drawn from the chapters 5.1 to 5.4, is that the substance formaldehyde (as formalin, a 44 wt% solution) as used by ANFCH as a raw material in the “Strecker” synthesis for Na_4EDTA, according to REACH may be seen as a “transported isolated intermediate”, which is used under “strictly controlled conditions” as described under Article 18 (4) [see Appendix 1]. This means that a registrant can provide reduced registration information according to Article 18 (2) if he confirms or states that he has received confirmation from both the manufacturer/importer and the user that the substance is manufactured and used under strictly controlled conditions as described under Article 18 (4) [see Appendix 1].
The other research questions, regarding the substance formaldehyde (as formalin, a 44 wt% solution) as formulated in paragraph 2.2 will be answered further in paragraph 5.7.

5.6 Identity of the substance and physical and chemical properties

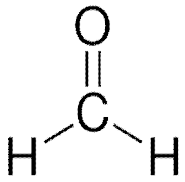
In order to be able to execute a proper Chemical Risk Assessment within REACH, it is necessary that the registrant gathers standard information on the substance to be registered, according to *Article 10* & *Annexes VI to XI*. All relevant and available information needs to be documented in both the technical dossier and the Chemical Safety Report, in the recommended reporting formats, which must be, for the technical dossier, IUCLID and for the Chemical Safety Report preferably the one mentioned in *Annex I.* In the next paragraphs, this has been done for the substance formaldehyde, from the point of view of the downstream user ANFCH.

5.6.1 Name and other identifiers of the substance

TABLE 1: SUBSTANCE IDENTITY

EC number:	200-001-08
EC name:	Formaldehyde
CAS number (EC inventory):	
CAS number:	50-00-0
CAS name:	Formaldehyde
IUPAC name:	Methanal
Annex I index number	605-001-00-5
Molecular formula:	CH_2O
Molecular weight range:	30.03 g/mol

Structural formula:



5.6.2. Composition of the substance

Table 2: Constituents

Constituent	Typical concentration	Concentration range	Remarks
Formaldehyde Water	44 wt% 56 wt%	35 – 50 wt% 50 – 65 wt%	ANFCH uses the typical concentration.

Table 3: Impurities

Impurities	Typical concentration	Concentration range	Remarks
Methanol Formic acid	impurity	impurity	Impurity

Table 4: Additives

Constituent	Function	Typical concentration	Concentration range	Remarks
Methanol	used for stabilization	0 wt%	1 – 2.0 wt%	ANFCH uses the typical concentration.

5.6.3 Physico chemical properties

Table 5: Overview of physicochemical properties

PHYSICOCHEMICAL PROPERTIES FORMALDEHYDE (100%)		
PROPERTY	**VALUE**	**REMARKS**
Physical state (20 °C, 101.3 kPa)	Gas Liquid	pure water-free state formaldehyde solutions
Melting/freezing point	-117 °C	(- 118 to -92 °C) at 101.3 kPa
Boiling point	-19° C	(- 21 to -19 °C) at 101.3 kPa
(Relative) density	0,8153 g/cm^3 1,1 (air = 1)	pure substance (L) at -20 °C pure substance (G) at 25°C
Vapour pressure	5176 hPa (calc., measured 5185) 4378 hPa (calc., measured 4420)	vapour pressure at 25 °C; vapour pressure at 20 °C
Surface tension	73	mN/m at 20 °C
Water solubility	Very soluble	(400.000 - 550.000 mg/l at 25 °C)
Partition coefficient log K_{ow} n-octanol/water (log value)	-0.65	(-0,75 to 0,35) Log P_{ow} 0.35, at 25 °C
Partition coefficient log K_{oc} organic C/water (log value)	0.70 - 1.57,	
Henry's Law constant	2.2 x 10^{-2} to 3.4 x 10^{-2}	(Pa.m^3/mol, at 25 °C)
Flash point	60° C	(32 – 61 °C)
Flammability	flammable	
Explosive properties	Lower explosion limit: 7 vol.% Upper explosion limit: 73 vol.%	[CH_2O]: 87 g/m^3 , at 20 °C [CH_2O]: 910 g/m^3 , at 20 °C
Auto flammability	430° C	Self-ignition temperature
Oxidising properties	Not oxidising	
Granulometry	Not applicable	substance is a liquid
Stability in organic solvents and identity of relevant degradation products	Normally considered stable and inert	
Dissociation constant (pKa)	13.27	(at 25 °C)
Viscosity	1.82	mPa s bij 60 C
Reactivity towards container material	Formaldehyde reacts violently with strong oxidising agents, causing risk of fire and explosion. Reacts with strong bases, producing hydrogen gas which is flammable. Reacts violently with acrylonitrile. Development of hazardous gas or vapour when formaldehyde comes in contact with hydrochloric acid: dichlorodimethylether Releases toxic fumes of carbon monoxide and carbon dioxide when heated to decomposition.	
Thermal stability	Decomposition when heated	decomposition products: methanol, carbon monoxide, water

5.6.4 Manufacture and identified uses

Table 6: Description of identified uses

Identified use	Sector of Use (SoU)	Preparation Category (PC)	Process category (PROC)	Article category (AC)
Raw material in the Strecker synthesis for Na_4EDTA	SU3, SU8, SU9	PC12, PC20, PC30, PC35	PROC3	Not applicable

Uses advised against: Formaldehyde as such or in preparations or as substance in articles should not be placed on the market for professional or consumer use.

5.6.5 Classification and labelling[1]

CLASSIFICATION AND LABELLING IN ANNEX I OF DIRECTIVE 67/548/EEC

Classification

The substance [C ≥ 25 %] is classified:

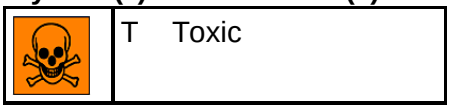
- T R23/24/25
- C R34:
- Carc.Cat.3 R40
- Sensitisation R43

Labelling

Indication of danger: carcinogenic category 3
R-phrases: R23/24/25, R34, R40, R43
R23/24/25: Toxic by inhalation, in contact with skin and if swallowed
R34 : Causes burns
R40 : Limited evidence of a carcinogenic effect
R43 : May cause sensitisation by skin contact

S-phrases: S26. S35. S36/37/39, S45
S26 : In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
S36/37/39 : Wear suitable protective clothing, gloves and eye/face protection .
S45 : In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
S51 : Use only in well-ventilated areas

Symbol(s) and Indication(s) of Danger



[1] The template will be updated once the Regulation on Classification, Labelling and Packaging of substances and mixtures (implementing the GHS) will be adopted.

Specific concentration limits:

Concentration :	Classification/Labelling :
C ≥ 25%	T; R23/24/25-34-40-43
5% ≤ C < 25%	Xn; R20/21/22-36/37/38-40-43
1% ≤ C < 5%	Xn; R40-43
0,2% ≤ C < 1%	Xi; R43

5.6.5. Self classification(s) and labeling

Table 7: Classification according to Directive 67/548/EEC criteria

Endpoints	**Classification**	**Reason for no classification**	**Justification for (non) classification can be found in section**
Explosiveness		Classification criteria not met	6.1
Oxidising properties		Classification criteria not met	6.3
Flammability		Classification criteria not met	6.2
Thermal stability		Classification criteria not met	
Acute toxicity		Classification criteria not met	5.2
Acute toxicity- irreversible damage after single exposure		Classification criteria not met	5.2
Repeated dose toxicity	**T**: R23/24/25: Toxic by inhalation, in contact with skin and if swallowed		5.6
Irritation / Corrosion	**C**: R34 : Causes burns		5.3.4 and 5.4.3
Sensitisation	R43 : May cause sensitisation by skin contact		5.5.3
Carcinogenicity	R40 : Limited evidence of a carcinogenic effect		5.8.3
Mutagenicity - Genetic Toxicity		Classification criteria not met	5.7.3
Toxicity to reproduction- fertility		Classification criteria not met	5.9.3
Toxicity to reproduction- development		Classification criteria not met	5.9.3
Toxicity to reproduction – breastfed babies		Classification criteria not met	5.9.3
Environment		Classification criteria not met	7.6

5.6.6. Environmental fate properties

Table 8: Study summaries

Method	Results	Remarks
Hydrolysis	Hydrolyses half-life at 20 °C, pH ca. 7 is 30h. In water formaldehyde undergoes essentially complete hydration to yield the gem-diol, methylene glycol	
Photodegradation		
	Indirect Photolysis half-life is about 1.7 days.	25 C
	Direct Photolysis half-life is about 4.1 hours	25 C
Biodegradition		
OECD 301D: Closed Bottle test	Formaldehyde is readily biodegradable in water (90% after 28 days) and in soil.	
Distribution		
Mackay Level I calculation	Formaldehyde primarily distributes to water. (water: 99% equilibrium distribution)	
Adsorption/desorption		
Log K_{oc}	Log K_{oc}:0.70- - 1.57, so <1.5. Therefore F. will be mobile in soil and not be sorbed by sludge in a seawage treatment plant.	
Acute toxicity to fish		
marine	6.7<96-h LC50 <1020 mg/l	Morone Saxatilis
fresh water	96-h LC50: 24.8 mg/l	Ictalurus Melas
Acute toxicity to daphnia		
	48-h EC50: 5.8 mg/l	Daphnia pulex
OECD 202/EU92/69 C2	14.7< 24-h EC50 <18.2 mg/l	Daphnia magna
OECD 202/EU92/69 C2	48-h EC50: 29 mg/l	Daphnia magna
Algal growth inhibition test		
3% cell grow inhibition	24-h EC50: 14.7 mg/l	Algae
O_2 production/consumption	24-h EC10: 3.6 mg/l	Algae
Activated sludge respiration inhibition test		
OECD 209/EU67/548 C3	3-h EC50: 20.4 mg/l. Formaldehyde was not toxic to waste-water bacteria at a concentration of ca. 2000 mg/l	
Bioaccumulation	Log Pow < 1; this indicates a low potential for bioaccumulation, which is confirmed by results of studies with shrimps and fishes.	Fish, shrimps

References:

1. WHO, IPCS, 89, 1989
2. WHO, CICAD, 40, 2002
3. UNEP, OECD SIDS, 2001
4. HPA, Compendium of Chemical Hazards, formaldehyde, 2009

5.6.7 Human health hazard assessment

Table 9: Study summaries

Method	Results
Toxicokinetics	F. is readily absorbed from the respiratory tract following inhalation and from the gastrointestinal tract following ingestion, but is poorly absorbed following dermal exposure. Inhalation or ingestion exposure of F resulted in only local absorption because F. is rapidly metabolised at the initial site of contact. So only negible amounts will reach the systemic circulation. F. is eliminated either by urinary excretion as formic acid or exhaled as CO_2.
Acute toxicity	
Oral,	LD_{50}: 600 -800 mg/kg bw; test on rats. LD_{50}: 260 mg/kg bw; test on guinea-pigs
Inhalation	LC_{50}: 497 mg/m^3, test on Mice (4h) LC_{50}: 578 mg/m^3, test on Rat (4h) LC_{50}: 984 mg/m^3, test on Rat (0.5h)
Dermal	LD_{50}: 270 mg/kg bw; test on rabbits.
Irritation	
In vivo skin, 37 % solution, 4h.	Mild to moderate; test on rabbits.
In vivo eye, 0.6 mg/m^3	Moderate; test on mice.
In vivo respiratory tract, 0.6 mg/m^3	Moderate; test on mice.
In vivo respiratory tract, 2.5–7 mg/m^3	Severe; test on rats.
Corrosivity	Study summaries for endpoints “sensitisation” and “irritation” indicate that formaldehyde is corrosive to the skin and eyes.
Sensitisation	
Skin, 10% solution	Sensitisation, test on Mice (hairless) [OECD 406]
Skin, 5 % solution	Sensitisation, test on Guinea pig.
Skin, 5%, 10%, 25% solution in aceton/olive oil	Sensitisation, test on Mice [Local Lymph Node Assay (LLNA)]
Respiratory tract, 10%, 25% 50% solution [in DMF]	No sensitisation, test on Mice.[immuno globulin E test]
Respiratory tract, 50% solution	No sensitisation, test on Mice [Lymph Node Cell culture]
Repeated dose toxicity	
Oral, 2-yrs drinking water test	NOAEC is 260 mg/l in drinking water (15-21 mg/kg/bw); test on rats
Inhalation	NOAEC is 1-2,5 mg/m^3 independent from exposure duration, test on rats. LOAEC is 2,5-7 mg/m^3 independent from exposure duration, test on rats. Marked Effect Concentration is 7 mg/m^3 ; expansion and severity of effects varies with duration of exposure, test on rats. (see paragraph 5.8, p. 28)
Dermal	Skin irritation NOAEC (mouse, dermal, 26 weeks) 0,1% Skin irritation LOAEC (mouse, dermal, 26 weeks) 0,5% Systemic effect NOAEC (mouse, dermal, 26 weeks) ≥ 1%
Mutagenicity	
AMES test; In vitro Chromosome aberration test,	F. has been tested for its genotoxic potential both *in vitro* and *in vivo* and, based on the results, is considered to be mutagenic at the site of contact.
Carcinogenicity	The International Agency for Research on Cancer (IARC, 2005) has concluded, on basis of a lot studies dealing with exposures to F. by inhalation, that there is sufficient evidence for the carcinogenicity of F. (nasal tumours) both in humans and in experimental animals.
Toxicity for reproduction	F. is not considered to be a reproductive or development toxicant.
Other effects	No other information available.

***References:**

1. WHO, International Programme on Chemical Safety [IPCS], nr. 89, 1989
2. WHO, Concise International Chemical Assessment Document [CICAD], nr. 40, 2002
3. UNEP, OECD SIDS, 2001
4. HPA, Compendium of Chemical Hazards, formaldehyde, 2009

5.6.8.

Table 8: Available dose descriptor(s) per endpoint for a certain substance as a result of its hazard assessment.

Endpoint		**Quantitative dose descriptor[2] (appropriate unit) or qualitative assessment**		**Associated relevant effect[3]**	**Remarks on study[4]**
		Local[5]	Systemic[6]		
Acute toxicity[7]	Oral	LD_{50}: 600 -800			Rat
	inhalation	LC_{50} : 497 LC_{50} : 578 LC_{50} : 984			Mice (4h) Rat (4h) Rat (0.5h)
Irritation/ Corrosivity	skin	37 % solution	NA[8]	Mild to moderate	Rabbit (4h)
	eye	0.6	NA	Moderate	Mice
	respiratory tract	0.6 2.5 – 7.4	NA	Moderate Severe	Mice Rat
Sensitisation	skin	10% solution 5 % solution 5%, 10%, 25% in aceton/olive oil	NA	Sensitisation Sensitisation Sensitisation	Mice (hairless) Guinea pig Mice, Local Lymph Node Assay (LLNA)
	respiratory tract	10%, 25% 50% solution in DMF 50% solution of F.	NA	No sensitisation No sensitisation	Mice Mice, Lymph Node Cell cult.
Repeated dose toxicity sub-acute/ sub-chronic/ chronic	oral	NOAEL 15-21 mg/kg.bw (male, female respectively)	dosages up to 82 [male] – 109 [female] mg/kg.bw in drinking water	hist. changes within the forestomach & glandular stomach increase in renal papillary necrosis	Wistar rat (2 years)
	Dermal	NOAEC 0.1 % LOAEC 0.5%	NOAEC ≥ 1%	skin irritation skin irritation systemic effect,	Mouse, 26 weeks mouse, 26 weeks mouse, 26 weeks
	inhalation	7,4 – 18,4 24,6 – 49,1		increase in lesions of nasal passages damage to trachea and larynx	Rat, 6 h/d, 5 d/w for 6 weeks Mice, 6 h/d, 5 d/w for 13 weeks
Mutagenicity	in vitro	F is able to induce genetic mutations and chromosomal aberrations in bacterial and mammalian cells			Ames Assay, chromosome aberration test, the TK-locus of mouse lymphoma L5178Y cells
	in vivo	Genotoxic effects after exposure are limited to the cells which are in direct contact with F..			epidemiological studies in occupationally exposed populations
Carcinogenicity	oral dermal inhalation	The International Agency for Research on Cancer (IARC, 2005) has concluded, on basis of a lot of studies dealing with exposures to F. by inhalation, that there is sufficient evidence for the carcinogenicity of F. (nasal tumours) both in humans and in experimental animals.			WHO, IARC 2005
Reproductive toxicity[9] fertility impairment	oral dermal inhalation	The International Agency for Research on Cancer (IARC, 1995) has concluded that "wether administered by inhalation, ingestion or the skin to various species, formaldehyde did not exert adverse effects on reproductive parameters or foetal development". Ever since, there have been developed no new opinions at this point of view, founded by a sufficient number of solid and scientific studies.			WHO, IARC 1995
Reproductive toxicity developmental toxicity	oral dermal inhalation				

2 NOAEL (NOAEC), LOAEL , T25, BMD(L)10 or any other dose descriptor; indicate whether this concerns a no or lowest observed effect level etc

3 In this column the relevant effect for which the dose descriptor is determined is provided

4 This column is for indicating whether data were available, whether the substance is classified for this endpoint, for shortly describing specifics of the study (e.g. 28-d gavage rat,

5 d/wk or 2-gen diet rat, 7 d/wk), and for indicating (additional) uncertainty in available data

5 Local exposure: units are mg/m3 for inhalation, and mg/cm2 or ppm for dermal exposure

6 Systemic: units are mg/m3 for inhalation, and mg/kg bw/day for oral and dermal exposure

7 In general, sublethal toxicity is a more rational starting point for acute toxicity than mortality data; information on acute toxicity may also be derived from e.g. repeated dose toxicity studies or reproductive toxicity studies

8 Not Applicable

9 These repeated exposure studies may also show relevant acute effects of the test substance; these should be accounted for under the endpoint acute toxicity

5.7 Exposures to formaldehyde and operations in compliance with REACH

In § 2.2 the following research questions, regarding to some aspects of REACH were formulated:

1. what is mentioned about the use of intermediates within REACH?
2. how can ANFCH be in compliance with these parts of REACH as efficiently and effectively as possible?
3. how can ANFCH prove that they will be in compliance with the REACH regulation regarding strictly controlled conditions in using intermediates ?
4. which uncertainties are important in estimating the risk of exposure to intermediates and how should ANFCH deal with these uncertainties?

These questions will now be answered for the raw material formaldehyde (as used by ANFCH as formalin, a 44 wt% solution).

REACH in terms of "transported isolated intermediates" and "strictly controlled conditions"

In chapter 5.5 the conclusion was drawn that the substance formaldehyde (as formalin, a 44 wt% solution) as used by ANFCH as a raw material in the "Strecker" synthesis for Na_4EDTA, according to REACH may be seen as a "transported isolated intermediates".
Also the conclusion was drawn that the conditions of use of formaldehyde within ANFCH meets the description of "strictly controlled conditions and rigorous containment", mentioned in REACH Article 18 (4).
So for the "identified" use of formaldehyde within ANFCH a registrant can provide reduced registration information according to Article 18 (2) if he confirms or states that he has received confirmation from the manufacturer/importer and the user that the substance is manufactured and used under strictly controlled conditions as described under Article 18 (4).
The terms "transported isolated intermediates" and "strictly controlled conditions" and related matters are described more in detail in Appendix 3.

ANFCH in compliance with REACH: performing the formalities as efficient and effective

ANFCH, as downstream user of formaldehyde [as a transported isolated intermediate] under "strictly controlled conditions", has the obligation under REACH to confirm to the registrant of the formaldehyde that within ANFCH:

- formaldehyde is used under "strictly controlled conditions" as a raw material in the "Strecker" synthese for Na_4EDTA, including a brief general description of this identified use.
- formaldehyde is rigorously contained by technical means during their whole lifecycle including manufacturing, purification, cleaning and maintenance of equipment, sampling, analysis, loading and unloading of equipment or vessels, waste disposal or purification and storage.
- procedural and control technologies are used to minimize emission and any resulting exposure.
- only properly trained and authorized personnel is allowed to handle formaldehyde.
- in case of cleaning and maintenance works, special procedures such as purging and washing are applied before the system is opened and entered
- in case of an accident and waste is generated, procedural and/or control technologies are used to minimize emissions and the result of exposure during purification or cleaning and maintenance.
- the handling procedures are well documented and strictly supervised by the site operator.

All these mentioned matters should naturally be guaranteed in the operations of ANFCH, e.g. by means of a preferably certified management system. As stated in paragraph 5.1 – 5.4, this is the actual situation.

As mentioned in paragraph 5.4, the operations within ANFCH are in complete agreement with these obligations. Moreover the management system of ANFCH has been certified for years according to ISO 9001 and ISO 14001 and within a short time also according to OSHAS 18001. Information gathered in paragraph 5.1 – 5.6 must be kept up-to-date and preferably documented in specific files. Filing of this information is important for the reduced registration information according to Article 18 (2).

Other [common] obligations for ANFCH, as downstream user of formaldehyde are to:

- follow the instructions in the safety data sheet of formaldehyde and in the exposure scenario(-s) which will be attached to this safety data sheet. Identify and apply appropriate measures to control the risks communicated in the safety data sheet.
- inform the supplier/ of any new information on hazards, including classification and labelling.
- communicate with the supplier/registrant information that might call into question the appropriateness of the risk management measures in any exposure scenario received.
- inform her own customers with the required and adequate information according to REACH.

ANFCH in compliance with REACH: the arguments

Measurements of exposure to formaldehyde have been executed by a certified consultant, under typical and representative circumstances for the jobs to be done (as mentioned in § 5.2, 5.3 and 5.4). Measurements [*with SEP-pack cartridges and using calibrated Gilian Gilair pumps, characterized by an extremely constant flow*] and analyses have both been executed according to NIOSH 2016 [2003]. Results have been evaluated according to NEN 689 ("*Leidraad voor de beoordeling van de blootstelling bij inademing van chemische stoffen voor de vergelijking met de grenswaarden en de meetstrategie", 1995*). Based on literature data, the sum of the systematic error in sampling and measurement and the accidental error in sampling is no more than 10-20%.
So this is an accurate way to determine the exposure to formaldehyde of the workers concerned.

As mentioned, exposure to formaldehyde is highest for the unloading operators. That is during uncoupling of the (rinsed) unloading hose of the tanker and during monitoring the unloading process. Measurements show that for the unloading operators the exposure to formaldehyde are relatively low (max. 33.3 % of the dutch 8h-TWA for formaldehyde*****) and short-term (most of the time 6,25 % of the working time with a maximum of 18,75% of the working time).
As also mentioned, during their 8-hours shift the process operators will stay and work 2 to 3 hours in the process area and 5 to 6 hours in the operator room.
Measurements show that for the process operators exposure to formaldehyde is relatively low (max. 13.3 % of the 8h-TWA for formaldehyde*****) and fairly short-term (max. 37,5 % of the working time).
Under normal circumstances other personnel will not get into contact with formaldehyde.
If this happens, it will only be for a short time being in the process area. So their exposure is titled "very low, compared to the TWA". So ANFCH is operating in compliance with both dutch labour legislation and REACH.

***)Occupational Exposure Limit: the dutch 8h-TWA for formaldehyde is 0.15 mg/m^3, the 15-min-STEL is 0.5 mg/m^3.**

REACH and uncertainties

Uncertainties are inherently linked to risk assessment (see Vermeire, paragraph 7.5). And as will be explained in paragraph 7.1 – 7.3 there are a lot of sources of uncertainties. In the risk assessment they should all be taken in account in a correct way in order to draw the right conclusion.

The main forms of uncertainty within REACH, as demonstrated in this and previous chapters, don't lie in determining of exposures or in gathering existing toxicity data. At least this applies in any case for isolated transported intermediates [*apart from the value and applicability of these existing toxicity data*]. The main forms of uncertainty within REACH manifest themselves in the risk assessment or in setting up the Risk Characterization Ratio (RCR, see § 7.2). This will happen while answering the question (in case of the RCR value > 1) whether sufficient valid toxicity data have been collected, or when additional toxicity data are needed [and if so, which ones]. And when determining how, e.g. through additional toxicity testing, the gap in knowledge and/or facts can be eliminated.
Within REACH, a tiered integrated risk and uncertainty assessment is chosen in order to prevent most of these kind of uncertainties, if possible in a fairly simple but standardized way, or at least to reduce these kind of uncertainties as much as possible and also to reduce animal testing and to save costs. This tiered assessment has been discussed more in detail in paragraph 4.3 and 4.4.

Discussion about uncertainty of formaldehyde toxicity in the open scientific literature

Since formaldehyde is water soluble, highly reactive with biological macromolecules at the site of contact and rapidly metabolized, adverse effects as a result of exposure, are observed [both in humans and in animals] primarily in those tissues or organs with which formaldehyde first gets into contact (i.e. the respiratory and gastrointestinal tracts following inhalation and ingestion, respectively). For obligate nose-breathers that will be [in case of inhalation] the nasal passages, for oral breathers the trachea and bronchi.

In sensitisation tests for the respiratory tract on mice [a Lymph Node Cell culture with a 50 % solution and an immuno globulin E test with 10%, 25% and 50% solutions in DMF] no sensitisation was found (see p. 26).

Chronic inhalation of formaldehyde at concentrations of 10 ppm (12 mg/m^3) and higher led to clear increases in nasal tumour incidence in rats. Most of the nasal tumours were squamous cell carcinomas. The damage of nasal tissue played a crucial role in the tumour induction process.
In contrast, no significant numbers of tumours were seen in mice and Syrian hamsters following chronic exposure to concentrations up to 14.3 or 39 ppm (17-36 mg/m^3), respectively (*WHO, 1989, 2002*).
For humans, there are no data available of the exact exposure level at which inhaled formaldehyde has a sensitizing effect. Once sensitisation has developed, short-time exposure to low concentrations is sufficient to cause an asthmalike response (*WHO, 1989, 2002*).
Formaldehyde is for humans one of the Hazardous Air Pollutants (HAP's), that may be etiologic factors in the induction and exacerbation of asthma. (*Leikauf, 2002*).

Above-mentioned facts seem to be in contradiction with each other.

Rats and mice breathe only through the nose while humans, especially during heavy physical work, show considerable mouth breathing. Both rats and mice respond to formaldehyde inhalation by a reduction in their minute volumes and respiratory rates. However, this protective mechanism occurs at a much lower formaldehyde concentration in mice than in rats and what's more mice are able to minimize the inhalation of formaldehyde more efficiently than rats, resulting in lower exposure in mice than in rats. Besides, differences in nasal anatomy will also effect exposure in a certain amount.
And it is well known that, in case of exposure to formaldehyde, concentration is more important than dose in determining the cytotoxic effects of formaldehyde on the nasal mucosa of rats (*WHO, 1989, 2002*).
And it is common knowledge that humans are not mice or rats of 75 kg. body weight (*Hartung, 2009*).

Both the lack of adequate toxicity tests for modelling the respiratory sensitisation in humans and the difficulties in using animal data for that purpose has been extensively discussed by Vermeire *et al* (2007).

Vermeire concludes with regard to the respiratory sensitisation:
REACH does not include testing requirements for respiratory sensitisation. A number of test protocols has been published to detect respiratory allergenicity of low molecular weight compounds, but none of these are validated nor are these widely accepted. Given lack of available (Q)SARs and *in vitro* tests for respiratory sensitisation, it is not possible to provide any additional guidance on the evaluation of non-testing data for respiratory sensitisation.
Therefore, the development of models and testing guidance for respiratory sensitisation should be stimulated. It might be possible to conclude in a Weight- of Evidence (WoE) assessment that chemicals that are negative in the Local Lymph Node Assay (LLNA) test for skin sensitisation, as well as being considered as not being skin sensitisers, can also be regarded as lacking the potential to cause allergic sensitisation of the respiratory tract.

In risk assessment, an important tool for characterizing and reducing uncertainty due to lack of knowledge is the Weight- of Evidence (WoE) process, usually carried out by experts.
Unfortunately, formal procedures and consistent terminology for WoE-processes are lacking.
International efforts are ongoing to improve this situation and Vermeire (2009) strongly recommends to support these initiatives.

Conclusion

From this discussion, and also taking into account the background exposure to formaldehyde, it can as yet not be excluded nor confirmed that exposure to formaldehyde, as it has been measured during normal operations, may cause some risk of allergic reactions and a minimal increase of risk of nasal cancer .
However as potential exposure has been minimized, and the exposure remains well below the TWA, it can be concluded that the conditions of REACH for strictly controlled conditions and rigorous containment are met.

Other aspects of uncertainties will be discussed in chapter 7.

6. EXPOSURE DURING THE APPLICATION OF NITRILES BY ANFCH

6.1 General

Nitriles are manufactured outside Europe exclusive for ANFCH (*& AkzoNobel Chemicals Ningbo co. ltd.*) by a joint venture of AkzoNobel, packed in big bags in closed containers and transported to ANFCH. These nitriles (solids) are used as raw materials in the production of sequestrant agents as an alternative to a route starting from cyanide, formaldehyde and an amine, which is known as the "Strecker" synthesis.

6.2 Unloading and storage of nitriles

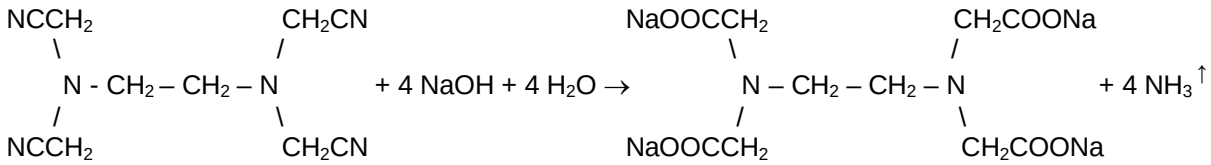
When the (20-feet steel sea-) containers arrive they are opened and unloaded using forklift trucks. The big bags are put in storage and from there transported on demand by forklift trucks to the process unit.

MOMENT OF EXPOSURE 6.2.1

Closed big bags containing solids are unloaded, put in storage and transported from there on demand to the process unit using forklift trucks without the need of manual human action. The operator in the forklift truck is not exposed to nitriles. During storage and transport, there is no exposure of any personnel or the environment.

6.3 Application of nitriles in the production process

Big bags with nitriles are hoisted up above a reactor and emptied under the influence of gravity into the reactor where the regulation amount of water is present. The base/trunk of the big bag is fixed over a funnel, so the whole content of the big bag is emptied into the reactor and there are no solids spread in the process area. Nitriles (supplied as "wet cake" containing 7 wt% water) have a non dusting character.
An exhaust system connected to the headspace of the reactor is in operation during emptying the big bag, so any material released in the free space of the stirring reactor is exhausted and emitted to air. Measurements show that this dust emission is 1 to 2 mg/m^3.
While stirring the reactor content, the "wet cake" with water is transformed into a slurry. This (non-volatile) slurry is pumped through a closed pipeline to another (closed) reactor with a stationary pump. In there, the slurry is converted ("saponified") into a sequestrant agent together with a caustic soda/ water mixture. This "saponification step" in the so called Singer synthesis is described in appendix 1.



N.B.: To illustrate the reaction EDTN (ethyleendiaminetetraacetonitrile) is used as an example but comment applies to all nitriles. From ethylenediaminetetraacetonitrile, sodium hydroxide and water the tetra sodium salt of ethyleendiaminetetraaceticacid (Na_4EDTA) is formed, with liberation of the by-product ammonia.

The process is controlled and monitored from the operator room, separated from the process area, by operators using an automated process control system (DCS). During their 8-hours shift the operators will stay and work 2 to 3 hours in the process area and 5 to 6 hours in the operator room.

Dumping of nitriles, including the handling of big bags, takes about ¾ hour each batch. Stirring and dissolving takes about 5 hours, pumping about ½ hour. The total charge time is about 7 - 8 hours. A maximum of 2 batches will be started every shift of 8 hours, each will take 3000 kg. of nitriles. During dumping of nitriles into the reactor, the operator uses PPE (personal protection equipment). Measurements using personal samplers[10] show that the total dust concentration in the process area, to which the operator is exposed during his work, will be between 1 and 1.4 mg/m^3.
The dust contains only limited amounts of nitriles because nitriles are supplied as a wet cake.

[10] Measurements have been done during handling of PDTN and NTAN, other nitriles in the form of wet cake, comparable to EDTN.

At the end of each batch samples are taken by draining process liquid from the reactor from a sample loop to check the quality of the product (an approximately 40 wt% solution in water). Because it is an irreversible reaction process, at that stage the reactor content is free of nitriles (below detection limit).

After finishing of a batch the reactor content is pumped into one of the storage tanks for finished products and from there delivered to “external downstream users" for their specific application(s) or to "internal downstream users" for use in one of the follow-up processes.
In case of product exchange the reactor, pump and piping are rinsed with water, which is discharged into the storage tanks for finished products.
The finished products will be delivered either in bulk or packed in 200-L. drums or 1000-L. IBC’s.

MOMENT OF EXPOSURE 6.3.1
During dumping of nitriles into the reactor, the operator uses PPE (personal protection equipment). Measurements show that the total dust concentration in the process area, to which the operator is exposed during his work [as mentioned 2 to 3 hours per shift], will be between 1 and 1.4 mg/m^3.

MOMENT OF EXPOSURE 6.3.2
At the end of each batch, sampling will be performed by draining process liquid from the reactor from a sample loop. By then, there are no nitriles in the process fluid; the exposure during sampling is zero.

MOMENT OF EXPOSURE 6.3.3
During maintenance of equipment, operators and maintenance workers will work according to established procedures incorporated in Standard Operation Procedures (SOP). This includes e.g. Safe Work Permits [including uncoupling, isolating and thoroughly pre-rinsing of the process equipment, the use of PPE and if necessary compressed air]. Exposure to formaldehyde during these activities is therefore virtually none.

MOMENT OF EXPOSURE 6.3.4
In case of an emergency the Site Emergency Plan will become effective and safety workers, well equipped with sufficient and appropriate PPE’s (if necessary also compressed air) will control the emergency.

MOMENT OF EXPOSURE 6.3.5
The final products DISSOLVINE E-39 or E-45 (respectively a 39 or 45 wt% solution of Na_4EDTA in water, in case of using EDTN as raw material) are free of nitriles (below detection limit). Therefore, further downstream in the chain, there will be no exposures to nitriles, neither for downstream users of Na_4EDTA nor for further processing within ANFCH. These products as such have no consumer applications.

6.4 Additional issues related to exposure to nitriles

Measurements
Measurements of exposure to nitriles (as mentioned in paragraph 6.3) have been executed by a certified consultant, under typical and representative circumstances for the jobs to be done.
Typical, because at the site of ANFCH the concerning process area is the only place where people could be exposed to nitriles originated from chemical processes.
Representative, because both the dumping of nitriles and the saponification step in the Singer synthesis have been executed in a standard way according to established procedures incorporated in Standard Operation Procedures (SOP).

Measurements [*using filters in a IOM-sample unit and calibrated Gilian Gilair pumps, characterized by an extremely constant flow, as personal monitor for the operator and separate as a spatial monitor in the process area*] and gravimetric analyses have both been executed according to MDHS 14/3 [2000]. Results have been evaluated according to NEN 689 (“*Leidraad voor de beoordeling van de blootstelling bij inademing van chemische stoffen voor de vergelijking met de grenswaarden en de meetstrategie”, 1995*). Based on literature data, the sum of the systematic error in sampling and measurement and the accidental error in sampling is no more than 10-20%.
So this is an accurate way to determine the exposure to nitriles of the workers concerned

Assessment if nitriles could be considered as “transported isolated intermediates”
According to REACH [article 3 (15)], an *intermediate* is defined as:

> ”*a substance that is manufactured for and consumed in or used for chemical processing in order to be transformed into another substance(s)*”

Intermediates should not be present in the final manufactured substance (except possibly as an impurity).

Under REACH different types of intermediates are defined:

- Non-isolated intermediates
- Isolated intermediates
  - * On-site (non transported) isolated intermediates
  - * Transported isolated intermediates

> **A non-isolated intermediate** is *an intermediate that during synthesis is not intentionally removed (except for sampling) from the equipment in which the synthesis takes place.*
> *Such equipment includes the reaction vessel, its ancillary equipment, and any equipment through which the substance(s) pass(es) during a continuous flow or batch process as well as the pipework for transfer from one vessel to another for the purpose of the next reaction step, but it excludes tanks or other vessels in which the substance(s) are stored after the manufacture* (*Article 3 (15)(a)*).
>
> **On-site isolated intermediate** means *an intermediate not meeting the criteria of a non-isolated intermediate and where the manufacture of the intermediate and the synthesis of (an)other substance(s) from that intermediate take place on the same site, operated by one or more legal entities (Article 3 (15)(b)).*
>
> **A site** means *a single location, in which, if there is more than one manufacturer of (a) substance(s), certain infrastructure and facilities are shared (Article 3(16)).*
>
> **A transported isolated intermediate** is *an intermediate not meeting the criteria of a non-isolated intermediate and transported between or supplied to other sites (Article 3 (15)(c)).*

It should be concluded that the substance nitriles as used by ANFCH as a raw material in the “Singer” synthesis for Na_4EDTA, according to REACH may be seen as a “transported isolated intermediate”.

Assessment if nitriles is used under “strictly controlled conditions”
It should be evaluated if the following conditions, as detailed in REACH Article 18(4), are in place at the site of ANFCH during the production processes for EDTA,:

(a) the substance is rigorously contained by technical means during its whole lifecycle including manufacture, purification, cleaning and maintenance of equipment, sampling, analysis, loading and unloading of equipment or vessels, waste disposal or purification and storage; (*Appendix 3, section 9. “Rigorous containment of the substance”*)
(b) procedural and control technologies shall be used that minimise emission and any resulting exposure; (*Appendix 3, section 10, “Procedural and control technologies to minimise emission and any resulting exposure”*)
(c) only properly trained and authorised personnel handle the substance; (*Appendix 3, section 11, “Handling of the substance by trained personnel”*)
(d) in the case of cleaning and maintenance works, special procedures such as purging and washing are applied before the system is opened and entered;
(e) in cases of accident and when waste is generated, procedural and/or control technologies are used to minimise emissions and the resulting exposure during purification or cleaning and maintenance procedures; (*Appendix 3, section 12, “Cases of accident and when waste is generated”*)
(f) substance-handling procedures are well documented and strictly supervised by the site operator.

These aspects will be evaluated in the next sub-paragraphs.

Identification of potential emissions to the workplace
Nitriles are supplied as "wet cake”. Big bags are mechanically unloaded from the container, put in and taken out of storage and transported to the process unit without the need of a direct human action. During storage and intern transport with a forklift truck, there is no exposure of any personnel to nitriles.

Dumping of nitriles into the reactor, including the handling of big bags, takes ca. ¾ hour. During this, the operator uses PPE (personal protection equipment). Stirring and dissolving take about 5 hours and pumping of the slurry ca. ½ hour. Total batch time is about 7 - 8 hours.
A maximum of 2 batches will be started every shift of 8 hours, each will comprise ca. 3000 kg nitriles. Measurements using personal samplers[11] show that the total dust concentration in the process area, to which the operator is exposed during his work [2 to 3 hours per shift], will be between 1 and 1.4 mg/m^3. The dust contains only limited amounts of nitriles because nitriles are supplied as a wet cake. At the end of each batch, sampling will be performed by draining process liquid from the reactor from a sample loop. At this stage there are no nitriles in the process liquid (below detection limit). Exposure of an operator to nitriles during sampling is virtually none.

[11] Measurements have been done during handling of PDTN and NTAN, other nitriles in the form of wet cake, comparable to EDTN.

During maintenance of the process equipment, operators and maintenance workers will work according to established procedures incorporated in Standard Operation Procedures (SOP) including e.g. Safe Work Permits. This includes thoroughly pre-rinsing the plants and the use of PPE, including compressed air if necessary. The exposure to nitriles during these maintenance/cleaning activities is therefore virtually none.

In case of an emergency, the Site Emergency Plan will become effective and safety workers, well equipped with sufficient and appropriate PPE (if necessary also compressed air), will control the emergency.

The final products DISSOLVINE E-39 or E-45 (resp. 39 or 45 wt% solution of Na_4EDTA in water) are free of nitriles (below detection limit) and have no consumer applications. So there will be no exposure to nitriles further downstream in the chain, neither for downstream users nor for further processing within ANFCH.

Identification of potential emissions to the environment (air, wastewater, soil, etc.)
During storage, there is no exposure of the environment to nitriles.

When the big bag is emptied, an exhaust system, connected to the headspace of the reactor, is in operation. Any material released in the free space of the reactor is exhausted and emitted to air. Measurements show that the total dust emission to air is 1 to 2 mg/m^3. This amount of dust contains only limited amounts of nitriles because nitriles are supplied as a “wet cake”.

Due to the nature of the "wet cake" [as the nitriles are supplied], the transport and storage methods for nitriles and the application of enclosed systems and piping systems in the production process [made of appropriate materials (stainless steel) for this substances] combined with the specific production process, of which the control, recipe and monitoring is audited by the process computer, there will be no emissions of nitriles to the soil or waste water neither during storage nor during the production process.

Modelling estimations or available monitoring data during unloading en production
This is not considered to be necessary as exposure is very low compared to TWA.

Procedural and control technologies to minimize emission and resulting exposure
During operation, the operator will be in the process area for about 2 to 3 hours per shift. During dumping of nitriles into the reactor, the operator uses PPE (personal protection equipment), in this case workwear and gloves, safety shoes and helmet and a P2 breathing mask. Because nitriles are supplied as a wet cake, only a limited amount of nitriles will be present as dust particles.

Maintenance, according to established procedures, includes thoroughly pre-rinsing the plants and the use of PPE (personal protection equipment, including compressed air if necessary). The exposure to nitriles during these activities (maintenance/ cleaning) is therefore virtually none.

Due to the nature of the "wet cake" [as the nitriles are supplied], the transport and storage methods for nitriles and the application of enclosed systems and piping systems in the production process [made of appropriate materials (stainless steel) for this substances], combined with the specific production process of which the control, recipe and monitoring is audited by the process computer, there will be no emissions of nitriles to the work area, the soil or waste water, neither during storage nor during the production process.

In case of an emergency, the Site Emergency Plan will become effective and safety workers, well equipped with sufficient & appropriate PPE (if necessary also compressed air), will control the emergency.

Handling of substance by trained and authorized personnel
All people working at the Herkenbosch site must be well educated, well trained and authorized for the jobs they are doing. The Human Resources Department will check this continuously.

During loading and unloading, operation and maintenance of the process equipment, logistic personnel, operators and maintenance workers will work according to established procedures incorporated in Standard Operation Procedures (SOP) including e.g. Safe Work Permits. Operators and maintenance workers have to use PPE (personal protection equipment, including compressed air) if necessary.

The chemical processes are controlled and monitored from the operator room by operators using an automated process control system (DCS) and the operators are audited by the process computer.

In case of an emergency, the Site Emergency Plan will become effective and safety workers, well equipped with sufficient & appropriate PPE (if necessary also compressed air), will control the emergency.

6.5 Conclusions related to the raw material nitriles

The conclusion, which can and should be drawn from the chapters 6.1 to 6.4, is that the substance EDTN as used by ANFCH as a raw material in the saponification step of the “Singer” synthesis for Na_4EDTA, according to REACH may be seen as “transported isolated intermediates”, which is used under “strictly controlled conditions” as described under Article 18 (4) [see Appendix 1].
This means that a registrant can provide reduced registration information according to Article 18 (2) if he confirms or states that he has received confirmation from both the user and the manufacturer / importer that the substance is used and manufactured under strictly controlled conditions as described under Article 18 (4) [see Appendix 1].
The other research questions, formulated in paragraph 2.2, will be answered further in paragraph 6.7.

6.6 Identity of the substance and physical and chemical properties

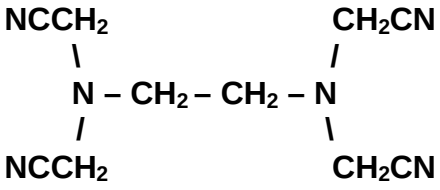
In order to be able to execute a proper Chemical Risk Assessment within REACH, it is necessary that the registrant gathers standard information on the substance to be registered, according to *Article 10* & *Annexes VI to XI*. All relevant and available information needs to be documented in both the technical dossier and the Chemical Safety Report, in the recommended reporting formats, which must be, for the technical dossier, IUCLID and for the Chemical Safety Report preferably the one mentioned in *Annex I.* In the next paragraphs, this has been done for the substance nitriles, as EDTN, from the point of view of the downstream user ANFCH.

6.6.1 Name and other identifiers of the substance EDTN

TABLE 9: SUBSTANCE IDENTITY

EC number:	227-290-3
EC name:	Ethylenediaminetetraacetonitrile
CAS number (EC inventory):	
CAS number:	5766-67-6
CAS name:	Ethylenediaminetetraacetonitrile
IUPAC name:	2-[2-[bis(cyanomethyl)amino]ethyl-(cyanomethyl)amino]
Annex I index number	605-001-00-5
Molecular formula:	$C_{10}H_{12}N_6$
Molecular weight range:	216.243 g/mol

Structural formula:



6.6.2 Composition of the substance

Table 10: Constituents

Constituent	Typical concentration	Concentration range	Remarks
EDTN Water	93 wt% 7 wt%	90 – 95 wt% 5 – 10 wt%	

Table 11: Impurities

Impurities	Typical concentration	Concentration range	Remarks
n.a.			

Table 12: Additives

Constituent	Function	Typical concentration	Concentration range	Remarks
n.a.				

6.6.3 Physico chemical properties

PHYSICOCHEMICAL PROPERTIES of EDTN		
PROPERTY	**VALUE**	**REMARKS***
Physical state	Solid	(20 °C, 101.3 kPa)
Melting/freezing point	159 °C	HPV EDTN: EPIWIN
Boiling point	427°C	HPV EDTN: EPIWIN
Relative density	1.26 g/cm^3	EC test A3
Vapour pressure	1 x 10^{-8} mBar	HPV EDTN: EPIWIN
Surface tension	Not applicable.	substance is a solid
Water solubility	1000 mg/l. 304, 299, 327 mg/l. at pH 5, 7, and 9	HPV EDTN: EPIWIN OECD Guideline nr. 105
Partition coefficient log K_{ow} n-octanol/water (log value)	-2.17 Pow < 1; Log Pow < 0	HPV EDTN: EPIWIN OECD 117
Partition coefficient log K_{oc} organic C/water (log value)	<1.5	OECD 121
Flash point	Not applicable.	
Flammability	Not applicable.	
Explosive properties	Not applicable.	EC test A14
Self-ignition temperature	Not applicable.	UN test N4
Oxidising properties	Not oxidising	
Granulometry	0.3 – 2.3 % of EDTN particles < 10 µm 10% < 45-60 µm, 50 % < 100-120 µm, 90% < 185-250 µm	only a small fraction of EDTN is respirable. NEN-ISO 13320-1
Stability in organic solvents and identity of relevant degradation products	Normally considered stable and inert	
Dissociation constant	Not applicable.	
Viscosity	Not applicable.	substance is a solid
Auto flammability	Not applicable.	
Reactivity towards container material	Reaction with strong oxidising agents. Reaction with strong acids and strong bases. Emits toxic fumes under fire conditions (nitrous gases (NOx)).	
Thermal stability	Stable under recommended storage and handling conditions	

*** References are part of the AkzoNobel tox files**

6.6.4 Manufacture and identified uses

Table 13: Description of identified uses

Identified use	**Sector of Use (SoU)**	**Preparation Category (PC)**	**Process category(PROC)**	**Article category (AC)**
Raw material in the saponification step in the Singer synthesis for Na_4EDTA	SU3, SU8, SU9	PC12, PC20, PC30, PC35	PROC3	Not applicable

Uses advised against: Avoid contact with strong oxidising agents, strong acids and strong bases. Under fire conditions EDTN emits toxic fumes (nitrous gases (NO_x)).

6.6.5 Classification and labelling[12]

CLASSIFICATION AND LABELLING IN ANNEX I OF DIRECTIVE 67/548/EEC

Classification

The substance is classified:

- for physical - chemical properties: n.a.
  for health effects: n.a.
  for the environment: n.a.

Labelling

Indication of danger: n.a.
R-phrases: n.a.
S-phrases: n.a.
Specific concentration limits: n.a.

6.6.6 Self classification(s) and labelling

Table 14: Classification according to Directive 67/548/EEC criteria

Endpoints	Classification	Reason for no classification	Justification for (non) classification can be found in section
Explosiveness		Classification criteria not met	6.1
Oxidising properties		Classification criteria not met	6.3
Flammability		Classification criteria not met	6.2
Thermal stability		Classification criteria not met	
Acute toxicity		Classification criteria not met	5.2
Acute toxicity- irreversible damage after single exposure		Classification criteria not met	5.2
Repeated dose toxicity		Classification criteria not met	5.6
Irritation / Corrosion		Classification criteria not met	5.3.4 and 5.4.3
Sensitisation		Classification criteria not met	5.5.3
Carcinogenicity		Classification criteria not met	5.8.3
Mutagenicity - Genetic Toxicity		Classification criteria not met	5.7.3
Toxicity to reproduction- fertility		Classification criteria not met	5.9.3
Toxicity to reproduction- development		Classification criteria not met	5.9.3
Toxicity to reproduction – breastfed babies		Classification criteria not met	5.9.3
Environment		Classification criteria not met	7.6

[12] The template will be updated once the Regulation on Classification, Labelling and Packaging of substances and mixtures (implementing the GHS) will be adopted.

6.6.7 Environmental and ecotoxicity fate properties

Table 15: Study summaries

Method	Results	Remarks	Reference*
Hydrolysis			
EPIWIN	No hydrolyses half-life can be estimated	EDTN	
EU method C.7	Hydrolyses half-life at 25 °C, pH 4, 7 and 9 is 5.3, 3.9 and 0.3 years respectively	PDTN	Brekelmans 1999
Photodegradation			
AOPWIN	Photodegradation half-life is estimated to be 4.6 hours	EDTN	
Biodegradition			
Modified Sturm test (EU-Method C.4-C/OECD 301B	PDTN is not readily biodegradable	PDTN	Desmares-Koopmans 1998
Distribution			
EEC Directive 92/69 Part C Publ.C383, 1992	EDTN primarily distributes to water and soil.	EDTN	
Adsorption/desorption			
HPLC method for Log K_{oc} according to OECD 121	Log K_{oc}<1.5: EDTN will be mobile in soil and not be sorbed by sludge in a seawage treatment plant.	EDTN	Vos, 2009
Acute toxicity to fish			
EPIWIN Level III fugative model	96-h LC50 >138 mg/l, Zebra fish (Danio rerio)	EDTN	Bogers 1998
OECD 203/EU92/69 C1	EC50 >100 mg/l, Zebra fish	PDTN	Bogers 1998
Acute toxicity to daphnia			
OECD 202/EU92/69 C2	48-h EC50 >100 mg/l.	PDTN	Bogers 1998
Algal growth inhibition test			
OECD 201/EU92/69 C3	72-h EbC50: 60 mg/l (cell grow inhibition) NOEC: 18 mg/l (NOEbC, grow inhibition)	PDTN	Bogers 1998
	72-h ErC50: 129 mg/l (grow rate reduction) NOEC: 32 mg/l (NOErC, grow rate inhibition)	PDTN	Bogers 1998
Activated sludge respiration inhibition test			
OECD 209/EU67/548 C3	PDTN was not toxic to waste-water bacteria at a concentration of ca. 100 mg/l.	PDTN	Desmares-Koopmans 1998
Chronic toxicity to Daphnia Magna (semi static test)			
OECD 211/EU67/548 C20	NOEC 10 mg/l; EC10 & EC50 (reproduction) 25.6 & 51.0 mg/l respectively; EC (parent survival) 148.6 mg/l.	PDTN	Gyimesi 2009
Bioaccumulation	Log Pow < 1; this indicates a low potential for bioaccumulation,		

*** References are part of the AkzoNobel tox files. Because of the similarity in structure of EDTN and PDTN, some toxicity tests were performed with PDTN.**

6.6.8 Human health hazard assessment

Table 16: Study summaries

Method	Results	Remarks	Reference*
Toxicokinetics	A toxicokenitic assessment is considered of limited value because of the acute oral and dermal toxicity of PDTN is low, the LD50 >2000 mg/kg bw and a 28-day toxicity study also revealed that PDTN has a low toxicity	PDTN	Groen, 1998
Acute toxicity			
Oral, EPA OPPTS 798.1175	LD50 > 5000mg/kg bw; test on Spague-Dawley rats.	EDTN	FitzGerald, 1993
Dermal, EPA OPPTS 798.1100	LD50 > 2000mg/kg bw; test on NZ white albino rabbits.	EDTN	FitzGerald, 1993
Oral, OECD 423, EU 67/548 B.1 tris	LD50 > 2000mg/kg bw; test on Wistar rats.	PDTN	Busschers, 1998
Dermal, OECD 402, EU 67/548 B.3	LD50 > 2000mg/kg bw; test on Wistar rats.	PDTN	Busschers, 1998
Irritation			
In vivo skin, EPA OPPTS 798.4470	No dermal reactions (4h-appl.); test on NZ white rabbits	EDTN	FitzGerald, 1993
In vivo eye, EPA OPPTS 798.4500	Slight to moderate redness, but no need for classification as an irritant; test on NZ white rabbits.	EDTN	FitzGerald, 1993
In vivo skin OECD 404, EU 67/548 B.4	No dermal reactions (4h-appl.); test on NZ rabbits	PDTN	Busschers, 1998
In vivo eye OECD 405, EU 67/548 B.5	Slight irritation, but no need for classification as an irritant; test on NZ white rabbits.	PDTN	Busschers, 1998
Corrosivity	Studies summarised for the endpoint “irritation” indicate that EDTN/PDTN is not corrosive to the skin or the eyes		
Sensitisation			
Skin (LLNA), EPA OPPTS 870.2600 OECD 429, EC 440/2008 B42	In the Local Lymph Node Assay (LLNA) EDTN was not considered to be a skin sensitiser; test on CBA mice.	EDTN	Van Huygevoort, 2009
OECD 407, EU 67/548 B.7	Due to several omissions and too low concentrations used during the sensitisation phase (no irritation was observed at all), it cannot be concluded or excluded wether or not the test material is a skin sensitiser.	PDTN	Busschers, 1998
Repeated dose toxicity			
Oral, OECD 407, EU 67/548 B.7	NOAEL is 200 mg/kg/day; 28-day test on SPF-bred Wistar rats.	PDTN	De Hoog, 1998
Mutagenicity			
AMES test, OECD 471 & 472, EU 67/548 B.13 & B.14	PDTN is not mutagenic in the salmonella typhimurium reverse mutation assay and in the Escherichia coli reverse mutation assay.	PDTN	Verspeek-Rip, 1998
In vitro Chromosome aberration Test, OECD 473, EU 67/548 B.10	PDTN is not glastogenic under the experimental conditions of this test.	PDTN	Bertens, 1998
Mouse Lymphoma Assay, OECD 476	PDTN was not mutagenic at the TK-locus of mouse lymphoma L5178Y.	PDTN	Steenwinkel, 2009
Carcinogenicity	PDTN did not induce mutagenicity in *in vitro* and *in vivo* studies. Systemic carcinogenicity is not expected to occur because in the body PDTN/EDTN is not expected be systemically available under normal handling and use conditions. Finally, no suitable studies are available to assess the risk on local carcinogenic effects.	PDTN	
Toxicity for reproduction			
OECD 421	NOAEL is 500 mg/kg (reproductive toxicity) NOAEL is 250 mg/kg (maternal and paternal toxicity); oral gavage tests on Sprague-Dawley rats.	EDTN	Ryan, 2007
Other effects	No other information available.		

- *** References are part of the AkzoNobel tox files. Because of the similarity in structure of EDTN and PDTN, some toxicity tests were performed with PDTN.**

Table 17: Available dose descriptor(s) per endpoint for a certain substance as a result of its hazard assessment.

Endpoint		**Quantitative dose descriptor[13] (appropriate unit) or qualitative assessment**		**Associated relevant effect[14]**	**Remarks on study[15]**
		Local[16]	Systemic[17]		
Acute toxicity[18]	oral	LD_{50} >5000 mg/kg bw			test on rat
	inhalation	n.a.			See 6.7.3: only a small fraction is considered respirable
	dermal	LD_{50} >2000 mg/kg.bw			test on rabbbit
Irritation/ Corrosivity	skin		NA[19]	Non-irritant	test on rabbbit (Akzo Nobel E-file)
	eye		NA	Slightly irritating to eyes, not sufficient for classification	test on rabbbit (Akzo Nobel E-file)
	respiratory tract		NA		
Sensitisation	skin		NA	No skin sensitisation	Local Lymph Node Assay (LLNA)
	respiratory tract		NA		
Repeated dose toxicity sub-acute/ sub-chronic/ chronic	oral	NOAEL 200 mg/kg.bw			Test with PDTN on rats
	dermal	No data available.			
	inhalation	No data available.			
Mutagenicity	in vitro			Not mutagenic	PTDN in Ames Assay, in chromosome aberration test and at the TK-locus of mouse lymphoma L5178Y cells
	in vivo	No data available.			
Carcinogenicity	oral	No data available. There is one literature reference which indicates dat EDTN could possibly be active as a anti-cancer agent.			
	dermal				
	inhalation				
Reproductive toxicity[20] fertility impairment	oral	NOAEL: 500 mg/kg[21]			test on rat
	dermal	No data available.			
	inhalation	No data available.			
Reproductive toxicity developmental tox	oral	NOAEL: 250 mg/kg			test on rat
	dermal	No data available.			
	inhalation	No data available.			

13 NOAEL (NOAEC), LOAEL , T25, BMD(L)10 or any other dose descriptor; indicate whether this concerns a no or lowest observed effect level etc

14 In this column the relevant effect for which the dose descriptor is determined is provided

15 This column is for indicating whether data were available, whether the substance is classified for this endpoint, for shortly describing specifics of the study (e.g. 28-d gavage rat, 5 d/wk or 2-gen diet rat, 7 d/wk), and for indicating (additional) uncertainty in available data

16 Local exposure: units are mg/m3 for inhalation, and mg/cm2 or ppm for dermal exposure

17 Systemic: units are mg/m3 for inhalation, and mg/kg bw/day for oral and dermal exposure

18 In general, sublethal toxicity is a more rational starting point for acute toxicity than mortality data; information on acute toxicity may also be derived from e.g. repeated dose toxicity studies or reproductive toxicity studies

19 Not Applicable

20 These repeated exposure studies may also show relevant acute effects of the test substance; these should be accounted for under the endpoint acute toxicity

21 Not Applicable

6.7 Exposure to nitriles and operations in compliance with REACH

In § 2.2 the following research questions, regarding to some aspects of REACH were formulated:

1. what is mentioned about the use of intermediates within REACH?
2. how can ANFCH be in compliance with these parts of REACH as efficiently and effectively as possible?
3. how can ANFCH prove that they will be in compliance with the REACH regulation regarding strictly controlled conditions in using intermediates ?
4. which uncertainties are important in estimating the risk of exposure to intermediates and how should ANFCH deal with these uncertainties?

These questions will now successively be answered for the raw material nitriles.

REACH in terms of "transported isolated intermediates" and "strictly controlled conditions"

In chapter 6.5 the conclusion was drawn that the substance nitriles, illustrated by means of the example EDTN as used by ANFCH as a raw material in the saponification step of the "Singer" synthesis for Na_4EDTA, according to REACH may be seen as "transported isolated intermediates". Also the conclusion was drawn that the conditions of use of nitriles within ANFCH meets the description of "strictly controlled conditions and rigorous containment" as mentioned in REACH Article 18 (4).
So for the "identified" use of nitriles within ANFCH a registrant can provide reduced registration information according to Article 18 (2) if he confirms or states that he has received confirmation from the manufacturer/importer andthe user that the substance is manufactured and used under strictly controlled conditions as described under Article 18 (4).
The aspects "transported isolated intermediates" and "strictly controlled conditions" and the related matters are described more in detail in Appendix 3.

ANFCH in compliance with REACH: performing the formalities as efficient and effective

ANFCH, as downstream user of nitriles [as transported isolated intermediates] under "strictly controlled conditions", has the obligation under REACH to confirm to the registrant of the nitriles that within ANFCH:

- nitriles are used under "strictly controlled conditions" as a raw material in the saponification step of the "Singer" synthese for chelates including a brief general description of the identified use.
- nitriles are rigorously contained by technical means during their whole lifecycle including manufacturing, purification, cleaning and maintenance of equipment, sampling, analysis, loading and unloading of equipment or vessels, waste disposal or purification and storage
- procedural and control technologies are used to minimize emission and any resulting exposure.
- only properly trained and authorized personnel is allowed to handle the nitriles.
- in case of cleaning and maintenance works, special procedures such as purging and washing are applied before the system is opened and entered
- in case of an accident and waste is generated, procedural and/or control technologies are used to minimize emissions and the results of exposure during purification or cleaning and maintenance.
- in case of an accident and waste is generated, procedural and/or control technologies are used to minimize emissions and the results of exposure during purification or cleaning and maintenance procedures
- the handling procedures are well documented and strictly supervised by the site operator.

All these mentioned matters should naturally be guaranteed in the operations of ANFCH, e.g. by means of a preferably certified management system. As stated in paragraph 6.1 – 6.4, this is the actual situation.
As mentioned in paragraph 6.5, the operations within ANFCH are in complete agreement with these obligations. Moreover the management system of ANFCH has been certified for years according to ISO 9001 and ISO 14001 and within a short time also according to OSHAS 18001.
The information gathered in paragraph 6.1 – 6.6 must be kept up-to-date and documented in specific files. Filing of these is important for the reduced registration information according to Article 18 (2).

Other [common] obligations for ANFCH, as downstream user of nitriles are to:
- follow the instructions in the safety data sheet of nitriles and in the exposure scenario(-s) which will be attached to this safety data sheet. Identify and apply appropriate measures to control the risks communicated in the safety data sheet.
- inform the supplier of any new information on hazards, including classification and labelling.
- communicate to the supplier/registrant information that might call into question the appropriateness of the risk management measures in any exposure scenario received.
- inform her own customers with the required and adequate information according to REACH.

ANFCH in compliance with REACH: the arguments

Measurements of exposure to nitriles have been executed by a certified consultant under typical and representative circumstances for the jobs to be done (as mentioned in paragraph 6.3 and 6.4). Measurements [*using filters in a IOM-sample unit and calibrated Gilian Gilair pumps, characterized by an extremely constant flow, as personal monitor for the operator and separate as a spatial monitor in the process area*] and gravimetric analyses have both been executed according to MDHS 14/3 [2000]. Results have been evaluated according to NEN 689 ("*Leidraad voor de beoordeling van de blootstelling bij inademing van chemische stoffen voor de vergelijking met de grenswaarden en de meetstrategie", 1995*). Based on literature data, the sum of the systematic error in sampling and measurement and the accidental error in sampling is no more than 10-20%.
So this is an accurate way to determine the exposure to nitriles of the workers concerned.

As mentioned exposure to nitriles is highest for the process operators; this is during dumping of nitriles into the reactor. During their 8-hours shift, operators will stay and work 2 to 3 hours in the process area [*dumping of nitriles, including the handling of big bags, takes about ¾ hour each batch; a maximum of 2 batches will be started every shift of 8 hours*] and 5 to 6 hours in the operator room. Under normal circumstances other personnel will not get into contact with nitriles. If this happens, it will only be for a short time being in the process area. Therefore, their exposure is titled "zero" or "virtually none".
Measurements show that for the process operators the exposure to total dust are relatively low (max. 14 % of the dutch 8h-TWA for total dust*****) and fairly short-term (max. 37,5 % of the working time). Next to it, the dust contains only limited amounts of nitriles because nitriles are supplied as a wet cake. So ANFCH is operating in compliance with both dutch labour legislation and REACH.

***)The dutch 8h-TWA for total dust is 10 mg/m^3; there isn't lay down an occupational exposure limit (OEL) for nitriles.**

N.B.: According to Directive 67/548/EEC criteria there is no need for a classification for EDTN [see paragraph 6.6.5 & 6.6.6] so there is also no need to develop exposure scenarios for the use of EDTN.

REACH and uncertainties

Uncertainties are inherently linked to risk assessment (see Vermeire, § 7.5).
And as will be explained in paragraph 7.1 – 7.3 there are a lot of sources of uncertainties. In the risk assessment they should all be taken in account in a correct way in order to draw the right conclusion.

The main forms of uncertainty within REACH, as demonstrated in this and previous chapters, don't lie in determining of exposures or in gathering existing toxicity data. At least this applies in any case for isolated transported intermediates [*apart from the value and applicability of these existing toxicity data*].
The main forms of uncertainty within REACH manifest themselves in the risk assessment or in setting up the RCR. This will happen while answering the question (in case of the RCR value > 1) whether sufficient valid toxicity data have been collected, or when additional toxicity data are needed [and if so, which ones].
And when determining how, e.g. through additional toxicity testing, the gap in knowledge and/or facts can be eliminated.
Within REACH, there is chosen for a tiered integrated risk and uncertainty assessment in order to prevent most of these kind of uncertainties, if possible in a fairly simple but standardized way, or at least to reduce these kind of uncertainties as much as possible and also to reduce animal testing and to save costs.
This tiered assessment has been discussed more in detail in paragraph 4.3 and 4.4.
Other aspects of uncertainties will be discussed more in detail in chapter 7.

Herewith the research questions, regarding to the substance nitriles (as EDTN) and some very interesting and important aspects of REACH, are answered.

7 SOME POINTS OF ATTENTION AND BOUNDARY CONDITIONS

With regard to the results of this investigation, as described in chapter 5 and 6, some points of attention and some boundary conditions must be mentioned. They are expressed in the following paragraphs.

7.1 Production strategy for fine chemicals in common and in relation to REACH.

It should be noted that the chemical industry in Europe safely handles very high tonnages of chemical products every year. Because of the hazardous properties of some of these products it is important that attention is given to safety and risk reduction by ensuring that emissions are maintained as low as reasonably practicable. For this reason good engineering practices, safe working conditions and safe working practices have been developed on an industry basis. Chemicals produced in high tonnages are mostly manufactured in large manufacturing facilities of high integrity, and it is necessary to control inherent properties of some chemicals such as toxicity, flammability and explosiveness by operating continuous processes under strictly controlled conditions. This is true for the manufacturing of many basic chemicals. These production plants are designed to minimize emissions to the environment and exposure to workers.
In addition there are processes that are operated more in a batch mode and sometimes in a multi-purpose production facility, like for instance in the fine chemicals production.
Because of the very nature of the fine chemicals business, it would be expected that a wide range of substances would be produced in relatively small volumes. Usually for products with very specific applications, for example in pharmaceutical/healthcare and other similar areas.
For various reasons, it will be less likely that process installations will be specifically designed for a specific product and it will be more common that fine chemicals will be produced using aggregates or reaction equipment, which are multi-purpose. It follows that, dedicated completely closed systems will be uncommon, and it will be necessary for operators in this field to implement an appropriate balance of management systems and various technical control measures.
This is to ensure strictly controlled conditions in a practical and relevant manner, which takes full account of the circumstances.
Therefore there will be a greater need for flexibility and for situation-based risk assessment to define appropriate systems and control measures to enable confirmation of strictly controlled conditions.

Within ANFCH the strategy is aimed at production of [rather] basic chemicals in relatively high volumes with the character of fine chemicals using closed batch process equipment of high integrity. Dedicated for 2-7 chemical final products each, this is operated by highly educated process operators, using management systems and various technical and organisational control measures. This includes that they have to be able to execute chemical processes in a responsible manner, to produce high-quality final products and to enable confirmation of strictly controlled conditions. Like all chemical industries in the Netherlands the operations within ANFCH have to be in compliance with Dutch legislation on labour, environment and [external] safety like (in Dutch) de Wet Milieubeheer, de Wet Verontreiniging Oppervlaktewater, de Richtlijn Integrated Pollution Prevention Control, het Besluit Risico's Zware Ongevallen 1999, a lot of other forms of [local] legislation and also REACH, of course.

7.2 Remarks

The following remarks should be made regarding the approach of the registration of a, for that purpose qualified, raw material as a "transported isolated intermediate".

* Every manufacturer/importer is and will be obliged to gather comprehensive information on the properties of all substances produced or imported in quantities > 1 tonne per year and to submit the necessary information to demonstrate their safe use in a registration dossier to the European Chemicals Agency.

* Failure to register will mean the substance cannot be manufactured or imported into the EU market.
* The registration requirement applies to substances on their own, in preparations and in articles under special conditions (intentional release).
* An intermediate is usually a substance as mentioned before but depending on the identified intermediates [REACH article 3 (15)] different obligations and information requirements are applicable.
* Every identified use should be registered but it is not necessary, nor obliged to develop separate exposure scenarios for all types of identified use and to insert these all in the registration dossier of a substance.
* Each registrant will still be obliged:
  - to develop, minimally one exposure scenario for the substance to be registered, at least if it is classified as a hazardous substance, and
  - to supply and communicate this exposure scenario with matching Risk Management Measures to the downstream users, by means of extended Safety Data Sheets, and
  - to ensure that all other forms of identified use are included in the registration and that the downstream users are confirmed to have implemented the Risk Management Measures in their operations.
* Downstream users of chemicals must identify and apply the RMM's to control the risks communicated in the supplier's Safety Data Sheet. In reverse he must inform the supplier of any new information on hazards, including classification and labelling and communicate to the supplier/registrant information that might call into question the appropriateness of the RMM's in any exposure scenario received.
* Companies using substances subject to restrictions must respect the conditions of the restrictions.
* Both the manufacturer/importer and the downstream user still have the obligation to fulfill their duties and their mutual activities regarding to REACH and still have to communicate adequate with each other.

8 DEALING WITH UNCERTAINTY IN THE CHEMICAL SAFETY ASSESSMENT

8.1 Introduction

Any risk assessment always carries uncertainty with it. Sharp boundaries in decision schemes hide the uncertainty that is inherent in any risk assessment or environmental decision analysis. In order to make decisions on chemical safety, a decision to act or not act needs to be based on a boundary or measure of (no) effect, even if uncertainty is incorporated in the outcome of the assessment.
An evaluation of uncertainty therefore should assist in communicating these uncertainties to improve decision making in the light of the uncertainty associated with the outcome of the risk assessment.
It is important to have an overview of how uncertainty can be dealt with and which new elements could be addressed under REACH. Uncertainty touches on all aspects of the risk assessment:

- hazard assessment: how uncertain is the measure of (no) effect,
- exposure assessment: how uncertain is the exposure estimate
- risk characterization: how uncertain is the combination of exposure and effect in the risk quotient
- risk assessment: how to take decisions in the light of uncertainty
- risk communication: how to communicate the uncertainty considerations
- knowledge of risk(s): how to deal with [no] knowledge about background exposure to same substances
- combination of risks: how to deal with substances potentially involved in combination toxicology

8.2 Uncertainty in risk assessment

Risk characterisation in Chemical Safety Assessment is the quantitative estimation of the likelihood that adverse effects occur to man or the environment due to actual or predicted exposure to a toxic chemical.
The measure of risk that could be used is a point estimate: the Risk Characterization Ratio (RCR).
The RCR compares the result of the exposure and effects assessment.
For environmental endpoints, the RCR is the PEC/PNEC ratio (*quotient of the predicted environmental concentration and the predicted no-effect concentration for an endpoint*); for human populations, it is the ratio exposure /DNEL (*the quotient of the predicted exposure concentration or dose and the derived no-effect level*).

$$RCR = \frac{PEC}{PNEC} \text{ or } \mathrm{RCR} = \frac{\text{exposure}}{\mathrm{DNEL}}$$

Risk characterisation is the integration of the exposure and the effect assessment into a risk estimate. This phase of the Chemical Safety Assessment (CSA) is the most logical place to consider uncertainties that are noticed and recorded in the preceding phases of the CSA. Both hazard and exposure assessment (including risk management that may influence exposure) carry a degree of uncertainty that is integrated in the RCR. The uncertainty in the outcome of a CSA iteration is relevant information that can be used to decide if risks are adequately controlled or that too much uncertainty is associated with it that needs to be addressed in further iterations of the CSA.
Considering uncertainty in the CSA would be easy if the RCR would be a true risk level, i.e. it would directly indicate if risks are adequately controlled (e.g., if risk would fall below an agreed threshold risk level or risk probability). However, the RCR is not a true risk level. The risk quotient merely indicates that if the no-effects threshold is exceeded (PEC > PNEC or PEC > DNEL), we define this as risk, and if the no-effect threshold is not exceeded, no risk is expected. Sources of uncertainty and variability play a major role in risk assessment. These issues can be identified:

- Measurement uncertainties due to e.g. low sample size or measurement error
- Selection and presence of data, especially when there are known different values for DNELs or PNECs or when there is known no threshold (e.g. in the case of formaldehyde)
- Extrapolation of measurements to derive DNELs or PNECs
- Species to species
- Acute to Chronic
- Route to route extrapolation
- Variability in exposure (time and space)
- Variability in effects (intra- and interspecies) due to age, sensitivity, etc.
- Model uncertainty due to ignorance or error
- Scenario uncertainty: parameters that mimic future actions by society or management actions (‘what if’scenarios)

8.3 Additional elements of uncertainty in REACH

REACH contains additional elements of uncertainty due to alternatives, like QSARs, read-across and *in vitro* testing, that are advocated to reduce animal testing. An additional element is the inclusion of risk management measures in the Chemical Safety Assessment to ensure safe use. However, they can be addressed at a much more informed level on RMMs (Risk Management Measures), leaving some uncertainty on the efficiency of recommended RMMs for consideration. Additional uncertainty considerations in REACH are:

- Uncertainty on toxicity because alternative methods for toxicity testing have been used
- Uncertainty in the toxicity of preparations, even if, for the main components, toxicity data are available
- Uncertainty in the actual exposure data, which may cause unrealistic worst case exposure estimates in the chemical risk assessment
- Uncertainty in the effectiveness and efficiency of recommended Risk Management Measures.

8.4 Dealing with uncertainties

Uncertainties are inherently linked to risk assessments (see Vermeire, paragraph 8.5). And as we have seen in § 8.1 – 8.3 there are a lot of sources of uncertainties. In the risk assessment they should all be taken in account in a correct way in order to draw the right conclusion.
Not all toxicological tests will incorporate every health aspect and rule out all the negative effects. Infinitely many tests will not give infinitely more new knowledge. That's why within REACH is chosen for a tiered integrated risk and uncertainty assessment in order to reduce animal testing and to save costs.
Toxicologists have to execute the right toxicological test in the right way and have to interpret the results of those tests correctly. They have to review test results critically and the toxicological tests continuously, and, if necessary, they should not hesitate to develop new methods and new views (see paragraph 8.5.).
And it is common knowledge that humans are not mice or rats of 75 kg. body weight. (*Hartung, 2009*).

8.5 Recent literature on risk assessment, uncertainty and toxicology

Vermeire (PhD thesis, June 2009) investigated in what way the scientific process of risk assessment can improve decision-making, knowing that uncertainties are inherently linked to risk assessment. His investigation is built on two frameworks: the IPCS/WHO framework for Integrated Risk Assessment (IRA), a problem formulation approach, and the framework for Uncertainty Management of Walker *et all,* a methodology formulation approach.

The IPCS/WHO framework for Integrated Risk Assessment (IRA)
The most important of the received benefits of IRA are increased assessment efficiency with regard to data collection and methodology, increased cost-effectiveness of assessment activities in view of shared resources and increased coherence of assessment results in view of shared methodology and risk characterization.

In registering chemicals under REACH Vermeire recommends that industry will interact with regulatory bodies and other stakeholders in a problem formulation approach like IRA. The intensity of such communication, especially at registration, should be proportional to the complexity of the Chemical Safety Assessment, the degree of risk forseen and the degree of uncertainty due to lack of knowledge.
However, further demonstrations of the scientific, economic and regulatory benefits of the IRA approach are needed. He recommends to perform cost-benefit studies to regard.

The integration of information could also help to develop testing strategies with the aim of avoiding vertebrate testing where possible. An important aim of REACH, the reduction of the use of experimental animals, is an important driver towards integrated approaches combining knowledge from *in vivo, in vitro, in silico* experiments, exposure data and information on mechanisms of action across species.
Also now there is further investigation needed, to know when and how such integration will show a positive balance with regard to costs and animals saved.

The uncertainty management scheme can be regarded as an additional layer in the IRA framework

aiming to improve the management and communication of uncertainty in IRA decision-making processes. This IRA$^+$ framework, as named by Vermeire, stimulates interactions between risk assessors, decision-makers and stakeholders and facilitates the analysis and prioritisation of uncertainties, supported by robust tools for a tiered integrated risk and uncertainty assessment.

The framework for Uncertainty Management of Walker *et all.*
The Probalistic Risk Assessment (PRA) in the EU framework for risk assessment of industrial chemicals is feasible with currently available techniques.
PRA potentially gives better decision-support to risk managers, because it gains more quantitative insight into the possible outcomes in a risk assessment and the degree of cumulated conservatism in the deterministic risk assessment. Sensitivity analysis is able to reveal the relative impact of uncertainties in parameters on the final result, where the risk assessment can be improved in the most time- and cost-efficient manner and whether it is necessary and achievable to reduce the uncertainty further.
For a further implementation of PRA, it is necessary to build up experience. If the tiered REACH guidance is followed, PRA's on more substances will become available. Important research areas are the characterisation of both default and chemical specific distributions, used for exposure and effects input parameters and methods to address environmental and human variability in the CSA and to separately address variability, based on experimental data, and uncertainty due to lack of knowledge.

In uncertainty analysis a clear separation needs to be made between quantifiable and non-quantifiable uncertainties and between true uncertainty (lack of knowledge) and variability to be able to answer different risk questions. Secondly, it should be made very clear which uncertainties are included in the assessment and which are not.

In risk assessment, an important tool for characterizing and reducing uncertainty due to lack of knowledge is the Weight- of Evidence (WoE) process, usually carried out by experts. Unfortunately, formal procedures and consistent terminology for WoE-processes are lacking. International efforts are ongoing to improve this situation and Vermeire strongly recommends to support these initiatives.

An important difficulty in the application of the process and methodology is the knowledge gap. Both risk assessors and risk managers often are unfamiliar with these new approaches and have to learn new skills. This should first of all be solved by training both risk assessors and risk managers. It requires a strong IRA$^+$–process with a tiered approach, graphical support and high communication skills of both experts and risk managers. The guidance available should be extended by showing real-life applications. Experts and risk managers need to investigate together how to use the results of uncertainty analysis in decision-making and how to communicate these in a transparent way.

If process and methodology follow the direction as shown by Vermeire, decision-support will be more transparent, will lead to less communication problems and will improve the trust between various parties involved. Decisions which fully take into account the uncertainties in the assessments performed, including the influence of divergent opinions and assumptions of experts and stakeholders, will be better informed and will lead to transparent decisions which can be communicated clearly.

So far Dr. Th. G. Vermeire

Hartung (Nature, July 2009) gives specific from a toxicological point of view an approach of some aspects regarding to REACH [e.g. uncertainty, test methods, number of laboratory animals required, correlation between test results and real practice].
He concludes that "*toxicological studies search for a rare hazard with imperfect models*".
Some of the consequences of this toxicological studies are a lot of false-positive test results and the 'requirement' of a great number of laboratory animals. These false-positive test results could unnecessarily restrict the use of many substances, require large and expensive efforts to replace chemicals that are widely used and create unnecessary fears in consumers about previous exposure. Hartung stated that it is unlikely that researchers will suddenly produce new tools and design new methods with great accuracy.
He suggests as solution for the mid-term the use of "integrated testing strategies" [making the best use of the existing methods by combining them strategically], in which optimal use is first made of all existing information about substances and structurally similar substances, and then information is gained by approaches that do not involve animal testing, leading to targeted animal testing only if necessary.

REACH also calls for the integrated use of all methods and for the use of animals as a last resort, so REACH calls for more flexibility and for tailored approaches instead of the standard toxicological test guidelines of the last 80 years. So REACH will also be a key instigator of changes within toxicology. And as mentioned by Vermeire in his PhD thesis:

> "The integration of information could also help to develop testing strategies with the aim of avoiding vertebrate testing where possible. An important aim of REACH, the reduction of the use of laboratory animals, is an important driver towards integrated approaches combining knowledge from *in vivo, in vitro, in silico* experiments, exposure data and information on mechanisms of action across species."

For the long-term the current system of testing needs to change into a system based on modern methods. Therefore Hartung suggests to have a look at a new regulatory toxicology, originates from a combination of bioinformatics and biotechnological approaches that yield huge amounts of information. Three important technologies developed during the last decade have entered the field of toxicology: *'omics' technologies, imaging techniques and robotized testing platforms*.
Omics' technologies and *imaging methods* compile enormous sets of information about a single compound. The *testing platforms* allow high throughput of samples, enabling large numbers of substances to be tested under standardized conditions.Together the three technologies not only allow researchers to 'fish' for new biological markers of specific toxic effects but also increasingly allow the deduction of patterns (or signatures) that are characteristic of certain toxic effects.
By also harnessing advances in bioinformatics and in silico modelling, this information can be mined and then integrated with knowledge from other areas of the life sciences. Such integration of information will be particular important for investigating cellular pathways and should allow the cross-fertilization of ideas between toxicology and basic science.
The combination of biochemical knowledge of cellular pathways with metabonomics, proteomics and genomics is already advancing as systems biology; systems toxicology is a new subbranch of this field. Such a systems approach was put forward as "*a toxicology for the twenty-first century*" on behalf of the Environmental Protection Agency (EPA). One of the first results is formed by EPA's ToxCast™ program.
The main challenge is to design a new system of regulatory toxicology, instead of amending the current patched-together system by adding a new piece or to replace an old piece of the system. The dimension of such a project calls for a global programme.
The scientific challenge laid down by this new vision of toxicology should appeal to scientists and to the commercial providers of (toxicological) solutions.This process needs to give up the old system, to design a new system and to include standardization, validation and quality assurance of the new approaches, as well as the systematic integration of these approaches into testing strategies. The profusion of new concepts and technologies should be communicated between stakeholders. The latter is probably more important than the individual technological developments that are required.

So far Prof. Dr. Th. Hartung

Although from different scientific perspective, both Vermeire and Hartung make useful suggestions, which also overlap each other partially, and which could significantly improve the process of Risk Assessment under REACH. With this conclusion, the importance of both publications is well founded.

Vermeire gives useful recommendations to improve existing ways of thinking, executing activities and research programs related to the risk assessment methodology for industrial chemicals within REACH. *Hartung* suggests a very interesting and innovating approach for the toxicological research, which also will improve the risk assessment methodology for industrial chemicals within REACH. In his appeal for designing a new system of regulatory toxicology, Hartung argues implicitly for dealing in a proper way with uncertainties, for the integrated use of new toxicologic testing methods and not only use the already wellknown *in vivo, in vitro, in silico* experiments and for the use of animals as a last resort.

It is the collective responsibility of ECHA (European Chemicals Agency), the united (chemical) industry and the toxicological scientific world to develop further on the proposals of both scientists [*and other useful proposals*], to improve the existing ways of thinking, executing activities and research programs, all related to the risk assessment and to introduce the above mentioned innovating approach for the toxicological research and to incorporate these topics into the methods for risk assessment within REACH. Toxicology will then really be a valuable contribution to ensure a high level of chemicals safety and a competitive chemicals industry and to balance the 7 objectives, as mentioned on page 2, within the overall framework of sustainable development.

Hartung stated that it is a huge challenge to design a new system of regulatory toxicology including standardization, validation and quality assurance of the new approaches, with the systematic integration of these approaches into new testing strategies. In this context, what will keep us from replacing the established institutes with batteries of *in vitro* tests for that purpose? And why should we only use mammals as laboratory animals for modelling the health risks of humans? Very recently, it was suggested to use insects as moths and fruit flies instead of mammals as mice and rats, for an insect's immune system, specifically its haematocytes, closely resembles one part of the mammalian immune system, the neutrophils. It could mean sizeable savings of time, costs and animals *(Kavanagh, 2009*).

9 CONCLUSIONS

Based on two examples, Formaldehyde (44 wt% solution) and EDTN (Ethylenediamine-tetra-aceto-nitrile), both used as a raw material in the production of Na_4EDTA within ANFCH, it has been investigated how to fulfill the duties of both a registrant and a downstream user and their mutual activities and how to act and communicate regarding to REACH as efficient and effective as possible in a unequivocal way. For that purpose the following research questions, regarding to some aspects of REACH were formulated in paragraph 2.2:

1. what is mentioned about the use of intermediates within REACH?
2. how can ANFCH be in compliance with these parts of REACH as efficiently and effectively as possible?
3. how can ANFCH prove that they will be in compliance with the REACH regulation regarding strictly controlled conditions in using intermediates ?
4. which uncertainties are important in estimating the risk of exposure to intermediates and how should ANFCH deal with these uncertainties?

The four questions were amply discussed and answered respectively in chapter 5 for formaldehyde and in chapter 6 for nitriles, among which EDTN. Below a short resume of these chapters.

1. *The use of intermediates within REACH*

Within REACH [article 3 (15)]. an *intermediate* is defined as: "*a substance that is manufactured for and consumed in or used for chemical processing in order to be transformed into another substance(s)*". Under REACH different types of intermediates are defined:

- Non-isolated intermediates
- Isolated intermediates
  - * On-site (non transported) isolated intermediates
  - * Transported isolated intermediates

One can conclude that both the substances formaldehyde (as formalin, a 44 wt% solution) and nitriles, used by ANFCH as a raw material in the "Strecker" synthesis or otherwise the "Singer" synthesis for Na_4EDTA according to REACH may be seen as "transported isolated intermediates".

2. *ANFCH can be in compliance with these parts of REACH as efficiently and effectively as possible*

One can conclude that ANFCH is operating in compliance with both dutch labour legislation and REACH, using the substances formaldehyde (as formalin, a 44 wt% solution) and nitriles, respectively as a raw material in the "Strecker" synthesis and the "Singer" synthesis for Na_4EDTA.

3. *ANFCH can prove that they will be in compliance with the REACH regulation regarding strictly controlled conditions in using intermediates*

It has been established that the following conditions, as detailed in REACH Article 18(4), are in place at the site of ANFCH using the substances formaldehyde (as formalin, a 44 wt% solution) and nitriles, as a raw material in the "Strecker" synthesis or otherwise the "Singer" synthesis for Na_4EDTA:

(a) substances are rigorously contained by technical means during their unloading, storage and use as raw material
(b) procedural and control technologies are used to minimize emission and any exposure to substances.
(c) only properly trained and authorized personnel handle the substance.
(d) in case of cleaning and maintenance works, special procedures (like purging and washing), as part of Standard Operation Procedures, are applied before the system is opened and entered.
(e) in case of an accident and when waste is generated, procedural and/or control technologies are used to minimize emissions and the result of exposure during purification, cleaning and maintenance procedures.
(f) substance-handling procedures, incorporated in the Standard Operation Procedures (SOP), are well documented and strictly supervised by the site operator, in cooperation with the proces engineer, the production staff and the HSE dept.

As potential exposure has been minimized, and the exposure remains well below the TWA, it can be concluded that the conditions of REACH for strictly controlled conditions and rigorous containment are met.

4[a]. *The following uncertainties are important in estimating the risk of exposure to intermediates*

The main forms of uncertainty within REACH don't lie in determining the exposure to substances or in gathering existing toxicity data. At least this applies in any case for isolated transported intermediates.
Main forms of uncertainty manifest themselves in the risk assessment or in setting up the RCR. This will happen while answering the question (*in case of the RCR value > 1*) whether sufficient valid toxicity data have been collected, or when additional toxicity data are needed [*and if so, which ones*]. And when determining how (*e.g. through additional toxicity testing*) the gap in knowledge and/or facts can be eliminated.
Within REACH, a tiered integrated risk and uncertainty assessment is chosen in order to prevent most of these kind of uncertainties. If possible in a fairly simple but standardized way, or at least to reduce these kind of uncertainties as much as possible and also reduce animal testing and save costs.

This does not affect the problem, as outlined in detail in paragraph 5.8, for the uncertainty of formaldehyde toxicity in common and those for the respiratory sensitization in humans in particular.

4[b]. How should ANFCH deal with these uncertainties

As potential exposure has been minimized, and the exposure remains well below the TWA, it can be concluded that the conditions of REACH for strictly controlled conditions and rigorous containment are met.

Conclusions

It has been proven that it is possible to fulfill the duties of both a registrant and a downstream user and their mutual activities and communication regarding REACH in an efficient, effective and unequivocal way for the raw materials formaldehyde and nitriles at the site Herkenbosch of Akzo Nobel Functional Chemicals B.V..

By means of the approach of registration of a, for that purpose qualified, raw material as a "transported isolated intermediate", a registrant can provide reduced registration information according to Article 18 (2) if this registrant confirms or states that he has received confirmation from both the manufacturer/importer and the user (being in the EU or outside the EU), that the substance is manufactured and used under strictly controlled conditions (SCC's) as described under Article 18 (4), facts described in Appendix 3.
In that case both the registrant and the user are each liable for their own statement regarding the SCC's.
N.B.: the registrant is usually also the manufacturer/importer of the substance.

Benefits

The approach studied here:

- Is *fully in compliance* with REACH [see art. 18(2) & 18(4)] and other legislation.
- Is valid for *all substances* provided that the obligations of REACH art. 18(2) & 18(4) are fully met so it can also be applied for "substances of very high concern" such as CRM's, PBT's and vPvB's.
- Is as *efficient and effective* as possible with respect to the concerning application and, moreover, is *unequivocal*.
- Is *very feasible* and *affiliates to other duties* in the domain of HSE and RA..
- Demands relatively limited efforts of registrant, downstream user and authorities and entails relatively low costs.
- The above mentioned means that, given the situation and the practices at the site Herkenbosch, ANFCH could successfully use this method for many of its raw materials.
  The same is valid for a significant proportion of the raw materials created by a considerable part of the chemical industry.
  However, it should be proven every time, for each raw material, that this substance is manufactured and used under strictly controlled conditions (SCC's) as described under REACH Article 18 (4),

10 REFERENCES

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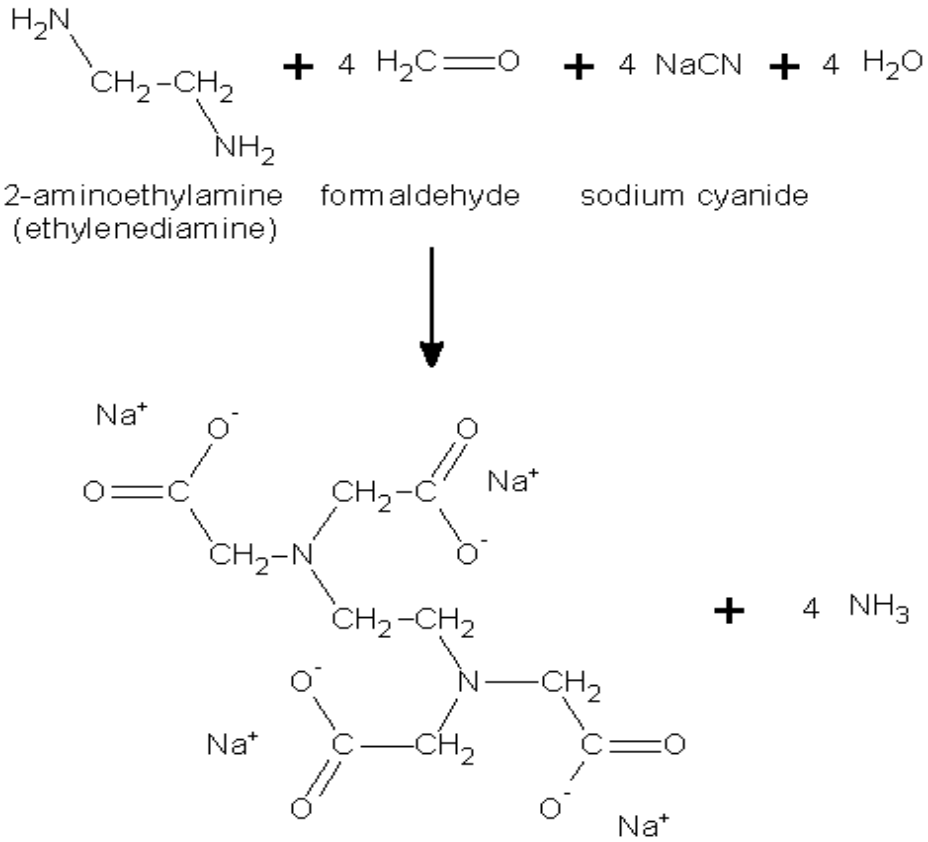
APPENDICES

APPENDIX 1: INDUSTRIAL SYNTHESIS OF EDTA

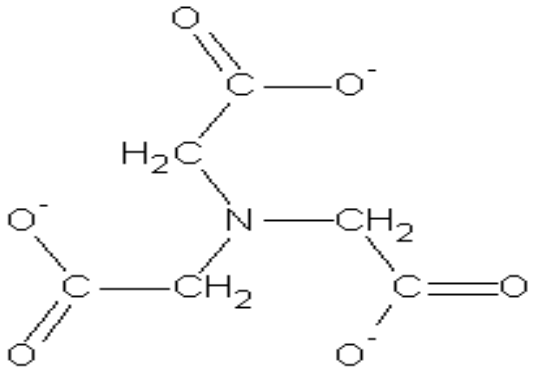
1: Single-step synthesis: The Strecker synthesis

The salt of the EDTA product is contaminated with the salt of NTA (nitrilotriacetic acid, another common chelator). This is the major method used commercially.



sodium salt of EDTA

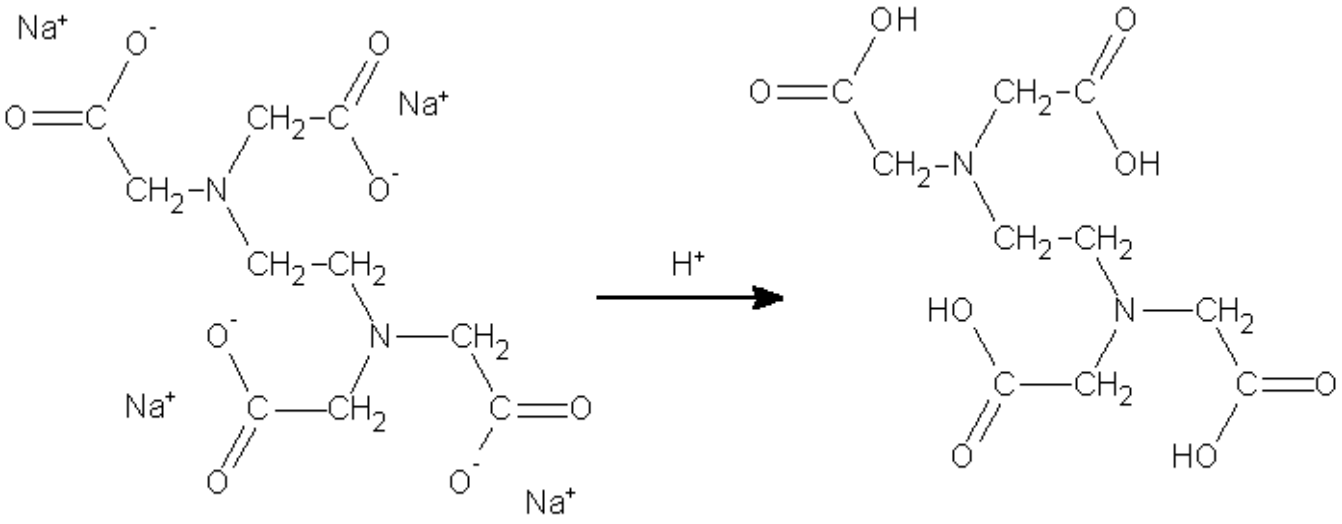
Most of the ammonia (NH_3) volatilizes and is recovered; however, some ammonia reacts with the reactants in the reaction above to produce the salt of NTA as a contaminant. NTA is another good metal chelator that is used for example in detergents.



salt of NTA produced as contaminant due to ammonia reacting

On acidification, the insoluble EDTA forms while the salt of the NTA remains in solution.

Conversion of salt to acid form is done with hydrochloric or sulfuric acids.

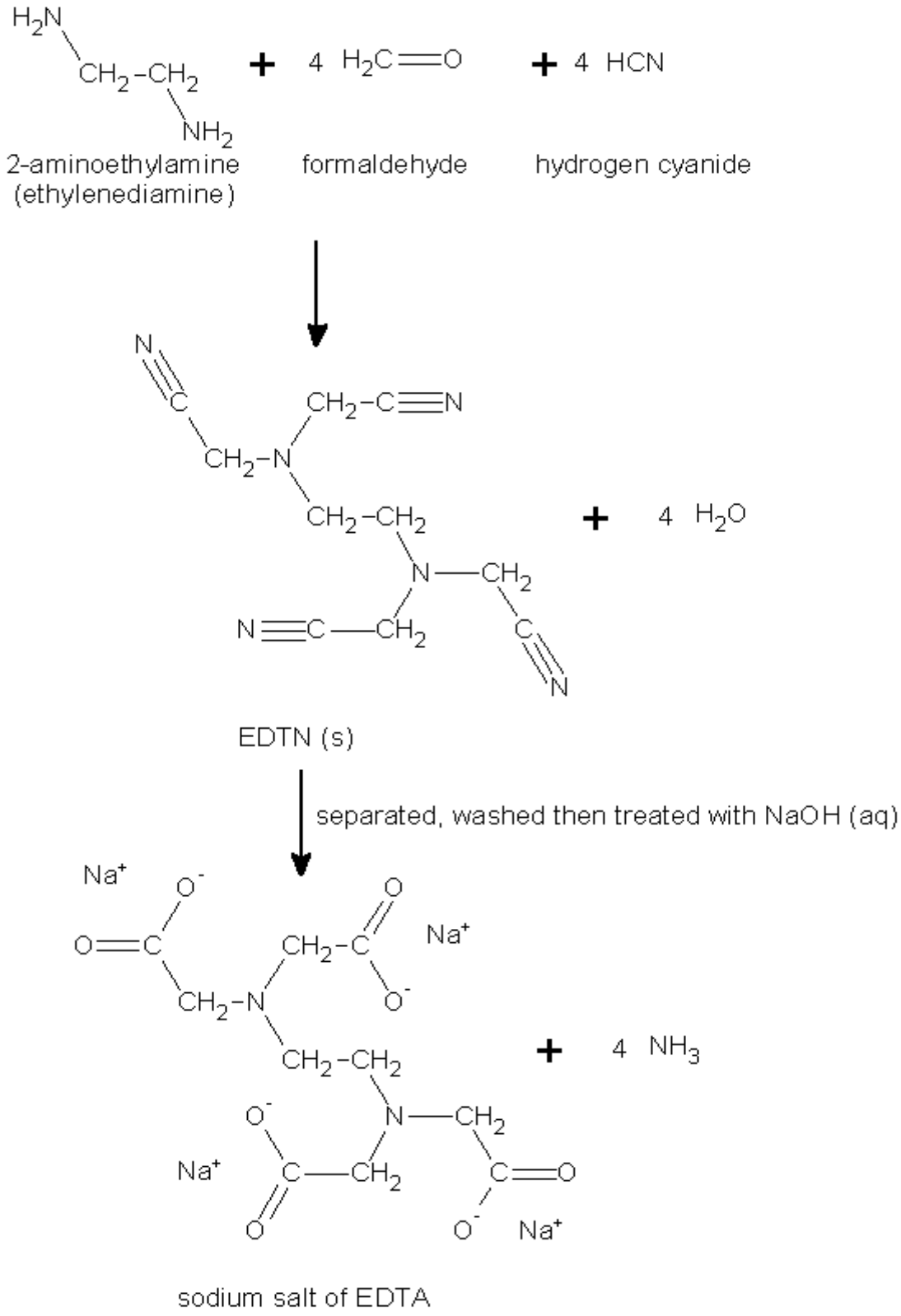


sodium salt of EDTA

EDTA

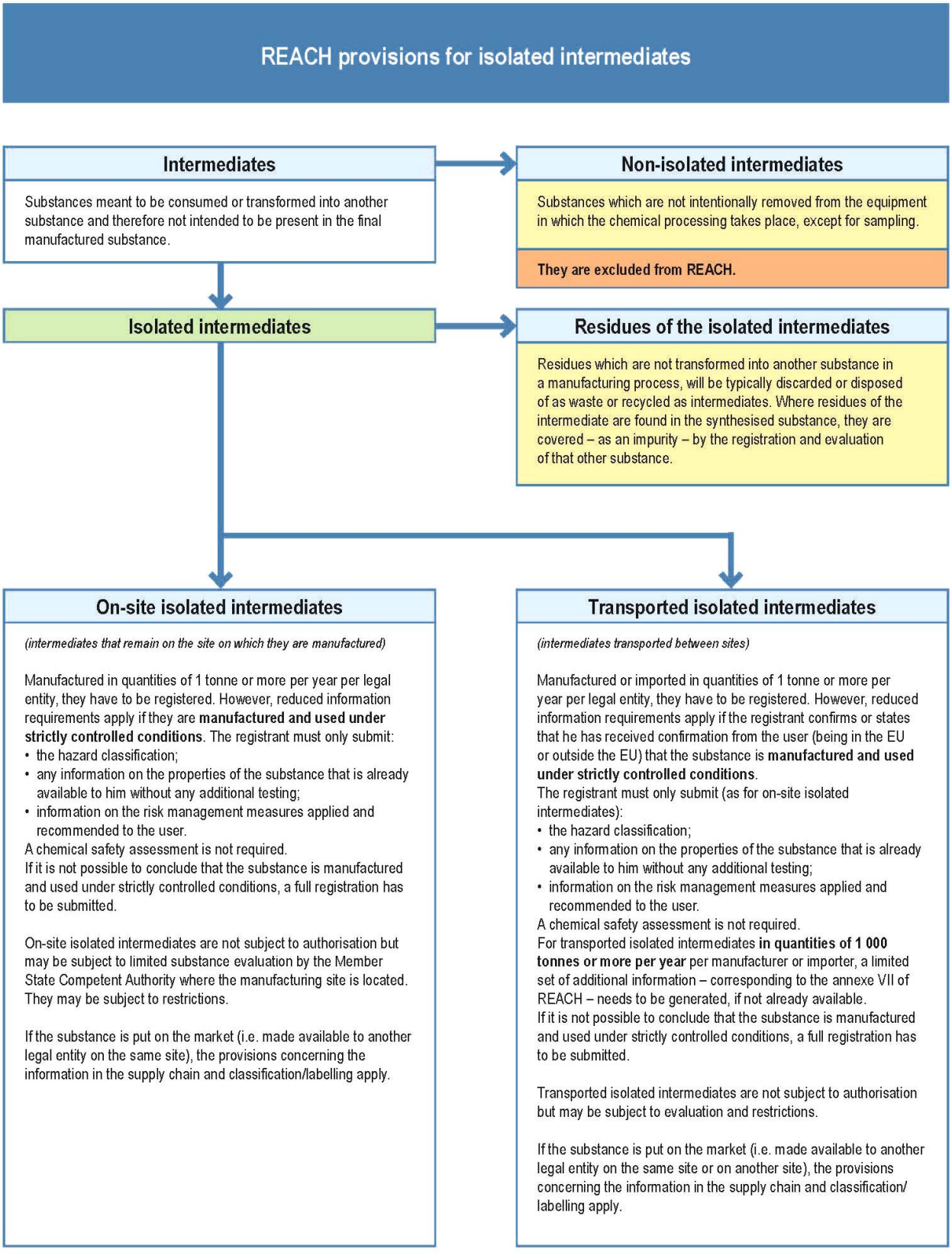
2: Two-step synthesis: the Singer synthese

This method allows for the production of a very pure form of the salt of EDTA.



Summarized from “Ethylenediaminetetraacetic Acid and Related Chelating Agents” in *Ullmann's Encyclopedia of Industrial Chemistry,* Vol. A10.

APPENDIX 2: PROCESSCHEME REACH & ISOLATED INTERMEDIATES



APPENDIX 3: INTERMEDIATES

1. On site isolated and transported isolated intermediates

According to REACH (this appendix is mainly a quotation from ECHA's *Guidance for intermediates*) an *intermediate* is defined as "*a substance that is manufactured for and consumed in or used for chemical processing in order to be transformed into another substance(s)*" [REACH article 3 (15)]. Therefore intermediates should not be present in the final manufactured substance (except possibly as an impurity).

Under REACH different types of intermediates are defined:

- Non-isolated intermediates
- Isolated intermediates
    * On-site (non transported) isolated intermediates
    * Transported isolated intermediates

> **A non-isolated intermediate** is *an intermediate that during synthesis is not intentionally removed (except for sampling) from the equipment in which the synthesis takes place. Such equipment includes the reaction vessel, its ancillary equipment, and any equipment through which the substance(s) pass(es) during a continuous flow or batch process as well as the pipework for transfer from one vessel to another for the purpose of the next reaction step, but it excludes tanks or other vessels in which the substance(s) are stored after the manufacture* (*Article 3 (15)(a)*).
>
> **On-site isolated intermediate** means *an intermediate not meeting the criteria of a non-isolated intermediate and where the manufacture of the intermediate and the synthesis of (an)other substance(s) from that intermediate take place on the same site, operated by one or more legal entities (Article 3 (15)(b)).*
>
> **A site** means *a single location, in which, if there is more than one manufacturer of (a) substance(s), certain infrastructure and facilities are shared (Article 3(16)).*
>
> **A transported isolated intermediate** is *an intermediate not meeting the criteria of a non-isolated intermediate and transported between or supplied to other sites (Article 3 (15)(c)).*

Depending on the identified intermediates different obligations and information requirements apply.

The lifecycle of an isolated intermediate begins with its manufacture (in practical terms, with its removal from the manufacturing process). This lifecycle ends with the use of the substance in the synthesis process for the manufacture of another substance.

Residues of the isolated intermediate, which are not transformed into another substance in a manufacturing process, will be typically discarded or disposed of as waste and channelled into waste management when not recycled as a non-isolated or isolated intermediate. Consequently, they no longer fall in the scope of REACH. Where residues of the intermediate are found in the synthesised substance, they are covered – as an impurity - by the registration and evaluation of that other substance.

2. Transported isolated intermediates

A manufacturer or importer of transported isolated intermediates in quantities of 1 tonne or more per year needs to register his substances. The information to be submitted for standard registration purposes (i.e. not reduced requirements due to strictly control conditions in place) is listed under Article 10 and detailed in section 1.8.1 of ECHA's *Guidance on registration*.
However a registrant of transported isolated intermediates can provide reduced registration information according to Article 18 (2) if he confirms or states that he has received confirmation from the user (being in the EU or outside the EU) that the substance is manufactured and used under strictly controlled conditions as described under Article 18 (4) and section 8. "*Strictly controlled conditions".* In that case both the registrant and the users are each liable for their own statement regarding the strictly controlled conditions.

3. Registration obligations and exemptions

* Article 2 (8) exempts intermediates from the general obligation to register substances. Instead, a manufacturer or importer of a transported isolated intermediate has to register his substance in quantities of 1 tonne or more per year under a different regime, as specified in chapter 3 of Title II of REACH.

- If the manufacturer or importer confirms that he is manufacturing and/or using the substance under strictly controlled conditions and he confirms himself or states that he has received confirmation from the users that the substance is used under strictly controlled conditions (section 8, "*Strictly controlled conditions"*) and the annual quantity of substance is less than 1000 tonnes, the information requirements on the substance's intrinsic properties (physicochemical, human health and environment properties) are reduced to available data (e.g. information he holds himself or that he can obtain from other sources) and only study summaries have to be submitted if a full study report is available (Article 18) (section 14, "Registration requirements for transported isolated intermediates").
- When manufactured and used under strictly controlled conditions and the annual quantity of substance is 1000 tonnes or more, the data requirements on the substance's intrinsic properties (physicochemical, human health and environment properties) as specified in Annex VII must be included in addition to the information required under chapter 3 of title II of REACH.
- Where strictly controlled conditions are not met, a full (standard) data package is required depending on the tonnage level (Articles 10 & 12).
- If the transported isolated intermediate is a monomer used for polymerisation, the reduced registration provisions for intermediates do not apply to the substance and the manufacturer has to proceed as for a "standard" substance (see ECHA's "*Guidance on registration"*).
- However, if a notification under Directive 67/548/EEC covering the relevant use has already been submitted by the manufacturer/importer, no registration is required (Article 24).
  The substance will be considered as registered and a registration number will be assigned by the Agency (Article 24).
- If the transported intermediate passes the 1000 t/y threshold, then the manufacturer/importer has to update the registration dossier and submit as a minimum the information required under Annex VII.

4. Classification and labelling

If the transported isolated intermediate is a phase-in substance to be registered the manufacturer/ importer must notify to the Agency the information related to its classification and labelling if (Article 113):

- he puts the substance on the market (i.e. he makes it available to another legal entity on the same site or on another site), and
- he has not already submitted a registration.

This has to be done before 1st December 2010 for substances already on the market at that date or, for substances that were not yet on the market on 1st December 2010, as soon as the substance is put on the market (Article 116).
For transported isolated intermediates registered before 1st December 2010 the classification and labelling will be reported in the registration dossier so that no separate notification is required.
If the transported isolated intermediate is a phase-in substance manufactured at less than one tonne per year, the manufacturer must notify to the Agency the information related to its classification and labelling if (Article 113):

- he puts the substance on the market (i.e. he makes it available to another legal entity on the same site or on another site), and
- the substance meets the criteria for classification as dangerous

This has to be done before 1st December 2010 for substances already on the market at that date or, for substances that were not yet on the market on 1st December 2010, as soon as the substance is put on the market (Article 116)
For non phase-in substances manufactured at 1 tonne or more per year a registration dossier has to be submitted in any case including the classification and labelling; in that case a notification is not necessary.

5. Dossier and substance evaluation

Manufacturer/importer must be aware that dossier and substance evaluation apply to transported isolated intermediates. Therefore, the Agency or, if there is no agreement between MSCA, the Commission may request additional information when it is conducting an evaluation. The manufacturer/importer must comply with any such request within the deadline set (see ECHA's "*Guidance on evaluation"*).

6. Authorisation/Restriction

* Intermediates are not subject to authorisation (i.e. Title VII – Authorisation - does not apply). This is also valid for intermediates used as monomers for the synthesis of polymers.
* Any manufacturer/importer or downstream user must check whether an intermediate is covered by any restriction in Annex XVII of REACH (Article 67).

7. Registration of isolated intermediates

Isolated intermediates (on-site as well as transported intermediates) are within the scope of REACH although specific requirements apply for their registration (Articles 2(8), 17, 18, and 19).

Manufacturers of on site isolated intermediates and manufacturers or importers of transported isolated intermediates in quantities of 1 tonne or more per year need to submit a registration dossier unless the substance is exempted from the registration provisions.

If the manufacturer or importer of a substance manufactures or imports the substance for other purposes than only the use as an intermediate, or if the manufacture or use(s) are not under strictly controlled conditions, then the manufacturer or importer needs to submit a “standard” registration dossier according to Article 10. In this situation, if part of the tonnage is manufactured and used under strictly controlled conditions, the registrant can submit one registration dossier covering all his tonnage. Information requirements for this registration dossier are based on the tonnage for non intermediate uses and for intermediates not used under strictly controlled conditions. The tonnage manufactured or imported as intermediate under strictly controlled conditions will not need to be taken into account for the information requirements of the registration dossier. Nevertheless the use as intermediate should be documented in the dossier, including the volume manufactured or imported for this purpose.
Fees must accompany any registration of intermediates. Fees are calculated independently for the use as intermediate under strictly controlled conditions (fees for intermediates) or the other uses (standard fees).

If the manufacturer or importer of the substance manufactures or imports it only for the use as an isolated intermediate under strictly controlled conditions (section 8, “*Strictly controlled conditions”*), then the manufacturer or importer can submit a registration dossier with reduced information requirements (according to Article 17 and 18) as described in section section 14, “*Registration requirements for transported isolated intermediates”*. However, this registration dossier has to contain all available existing information on the intrinsic properties of the substance.

The data requirements for the registration of isolated intermediates manufactured in quantities of 1 tonne or more per year depend on whether they are transported or not. For transported intermediates, those requirements depend on the manufactured or imported volume which is transported. Compared to the data requirements for the registration of a “standard” substance, there are reduced information requirements for isolated intermediates, as long as the registrant confirms that strictly controlled conditions are applied during manufacture and use of the substance on-site but also, in case of transported intermediates, that he has received confirmation from the user that strictly controlled conditions are applied on other sites (Articles 17(3) and 18(4)). In case of a transported isolated intermediate in quantities of more than 1000 tonnes per year, also the information specified in Annex VII of REACH should be included (Article 18 (3)). More guidance on how to calculate the tonnage is given in ECHA’s “*Guidance on registration”*.

For on-site isolated intermediates the information requirements on physicochemical, human health and environmental properties are limited to the data that is available to the manufacturer (e.g. information he holds himself or that he can obtain from other sources) without any additional testing. The registrant shall therefore gather all existing available information on physicochemical, human health or environmental properties of the substance for which he submits a registration dossier as required under REACH.

For transported isolated intermediates available existing information needs to be submitted as for on-site isolated intermediates, but a limited set of additional information needs to be generated, if not already available, if the annual tonnage exceeds 1000 tonnes/year as referred to in Article 18 and developed under section 14, Registration requirements for transported isolated intermediates.
The first task for the registrant is therefore to determine if the substance under investigation is an isolated intermediate manufactured and used under strictly controlled conditions and whether it is transported or not, in order to identify the information he has to provide in a registration dossier to fulfil his obligations.

8. Strictly controlled conditions

For both on-site and transported isolated intermediates the possibility to provide a reduced set of information for their registration applies when:

- For on-site isolated intermediates, the manufacturer confirms that the substance is only manufactured and used under strictly controlled conditions in that it is rigorously contained by technical means during its whole lifecycle (Article 17(3)).
- For transported isolated intermediates, the manufacturer or importer confirms himself or states that he has received confirmation from the user that the synthesis of (an)other substance(s) from that intermediate takes place on other sites under strictly controlled conditions detailed in Article18(4).
  For transported isolated intermediates that are manufactured in the EU the strictly controlled conditions shall apply both to the manufacture and use of the substance.

Therefore, in order to benefit from the reduced registration requirements the registrants have to first assess if their intermediates are handled under strictly controlled conditions on the sites of manufacture and uses. When filling his registration dossier using IUCLID5 the registrant must report if the substance is manufactured and used under strictly controlled conditions or not and can provide the confirmation of this (see section 15, Preparation of a registration dossier for isolated intermediates).
To assess if the intermediate is manufactured and used under strictly controlled conditions during its whole lifecycle, the registrant should evaluate if the following conditions, as detailed in Article 18(4), are in place:

(a) the substance is rigorously contained by technical means during its whole lifecycle including manufacture, purification, cleaning and maintenance of equipment, sampling, analysis, loading and unloading of equipment or vessels, waste disposal or purification and storage; (section 9. “Rigorous containment of the substance”)
(b) procedural and control technologies shall be used that minimise emission and any resulting exposure; (section 10, Procedural and control technologies to minimise emission and any resulting exposure)
(c) only properly trained and authorised personnel handle the substance; (section 11, “Handling of the substance by trained personnel”)
(d) in the case of cleaning and maintenance works, special procedures such as purging and washing are applied before the system is opened and entered;
(e) in cases of accident and where waste is generated, procedural and/or control technologies are used to minimise emissions and the resulting exposure during purification or cleaning and maintenance procedures; (section 12, Cases of accident and where waste is generated)
(f) substance-handling procedures are well documented and strictly supervised by the site operator.

The definition of strict control in Article 18(4) for transported isolated on-site intermediates can be used as a working basis for isolated on-site intermediates also. Article 18(4) provides a wider definition of strict control than Article 17(3) which is limited to criteria (a) and (b) of the above list. This does not mean that criteria (c) to (f) cannot also be appropriate criteria to determine strict control also for on-site isolated intermediates. This definition covers both: (i) normal operating conditions and (ii) non-routine operational circumstances such as maintenance and incidents.
For both types of intermediates, on the basis of the assessment and description of the conditions under which the substance is manufactured and/or handled on site(s) of both the manufacturer and the user in case of transported intermediates, the registrant has two possibilities:

- Submit a registration dossier containing the limited set of data requested for intermediates, provided that he concludes that the substance is manufactured and used under strictly controlled conditions.
- Submit a full registration dossier as described in Article 10, if he is not able to conclude that the substance is manufactured and used under strictly controlled conditions.

Strictly controlled conditions should be seen as a combination of technical measures that are underpinned by management systems. This approach to managing human health and environmental risks aligns with and acknowledges the existing regulatory obligations that impact on manufacturers of substances (e.g. control of accidents under Directive 96/82/EC3, Integrated Pollution Prevention and Control under Directive 96/61/EC4, occupational protection under the Chemical Agents Directive 98/24/EC5).

This approach includes training, process controls, management systems, monitoring, personal protective equipment (PPE) where combinations of 'hardware' and 'software' measures (using, in some cases, a hierarchy of preferences) strictly control risks.
However it should be kept in mind that the use of PPE, for example, should not have a prime role when determining whether workplace exposures to an intermediate are strictly controlled as the use of such measures alone generally cannot equate to strictly controlled conditions. It is recognised that PPE should be recommended and used especially in relation to sampling, maintenance and repair.
A full explanation of the strictly controlled conditions in place is not required in the registration dossier, however the assessment of the use(s) of any substance (or group of similar substances) as intermediate(s) should be documented within a company in order to show the adequacy of the measures as authorities may request such information which then must be made available. Where relevant, documentation for compliance with other legislative frameworks can also be referred to.

3 Council Directive 96/82/EC of 9 December 1996 on the control of major-accident hazards involving dangerous substances.
4 Council Directive 96/61/EC of 24 September 1996 concerning integrated pollution prevention and control
5 Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work.

The documentation may include:

- justification for the assignment of use as an intermediate to the substance, including customers' statements if a transported isolated intermediate;
- the relevant operating conditions;
- the risk management measures implemented in the company and recommended to external customers;
- the corresponding exposure considerations and
- reference or derivation of any relevant threshold value (e.g. Derived No Effect Levels (DNELs), Predicted No Effect Concentrations (PNECs)) including the relevant physico-chemical, toxicological and ecotoxicological data, including data from substance grouping where available.

The details of the risk management measures applied and recommended to the user, which reflect the strictly controlled conditions, should be included in the registration dossier. Existing legislative frameworks or industry standards can be used when documenting the risk management.

To facilitate the process for assessing whether strict control is achieved, Appendix 1 presents an indicative and non-exhaustive list of issues that could be considered.
This approach is only intended as a user-friendly tool to document the process of assessing the conditions of strict control. The actual process behind answering the questions involves considerable analyses by relevant people (e.g. site managers, engineers).
Although transported isolated intermediates require communication through the supply chain for confirmation that strictly controlled conditions are achieved, the process for documenting strict control does not require the interchange of information that could be seen to constitute confidential business information (e.g. fine detail of process technology and/or engineering, etc).

An example of a general format to document how the substance is manufactured and used in strictly controlled conditions is also proposed in Appendix 1, paragraph 15. This should contain information and justification on the relevant issues raised elsewhere in Appendix 1. Please also note that any information produced for the purpose of other pieces of legislation (e.g. worker protection legislation) can of course be used as an element to demonstrate strictly controlled conditions.

9. Rigorous containment of the substance

Rigorous containment is the combination of technical and procedural measures that ensure that exposure (whether to man or the environment) is reduced so that risks are strictly controlled.
It is applicable to handling of intermediates at any scale.
In every case, the successful management of risk is central to the concept of rigorous containment: when no hazard and risk information is available, then intermediates have to be treated as hazardous substances, with the accompanying need to ensure (and demonstrate) that emissions and exposure are minimised. When information on hazard is available for an intermediate, then the intermediate will be handled under appropriate conditions that ensure that any risks rising from handling the substance are strictly managed.

Consequently, the way that rigorous containment can be achieved may vary according to the knowledge of an intermediate's physicochemical and hazard properties.
The intermediate needs to be rigorously contained by technical means during its whole life cycle which includes the manufacture, the isolation of the intermediate out of the reaction mixture, if necessary further purification steps (e.g., distillation, re-crystallisation, filtration), cleaning and maintenance, sampling, analysis, loading and unloading of equipment/vessels, waste disposal/purification and storage, and the use in synthesis.
To be able to confirm and document in-house the rigorous containment of the substance, the registrant should characterise the processes during its whole life-cycle and equipment used to characterise the level of containment taking into account the properties of the substance. The description of these technical means and conditions should allow the identification of potential exposure of workers and the environment to the substance. One way to do this is to assure the necessary level of leakproofness of the different functional elements (pressurised vessels, seals, sacks, containers, drums, etc.) involved during the different steps of the whole process such as manufacture, transfer (filling, emptying, etc.) or sampling of the substance when potential emission could be expected to the workplace or the environment. For example, isolated intermediate packaging and containers should only remain open for short periods during equipment filling and emptying (via hose lines, pipe joints), during sampling (transfer from one container to another container via closed sampler) and when performing cleaning and maintenance. Consideration should be given to the transfer and management of the isolated intermediate in bulk through pipelines and dedicated bulk storage facilities. Containers or equipment open for any extended period of time should have suitable measures in place, which will be consistent with the characteristics and properties of the intermediate, e.g. efficient exhaust ventilation, to prevent any significant release of the substance into the immediate surroundings from the container. For companies operating batch processes in discontinuous equipment there may be other considerations, but the risk management adopted in these companies must also identify a suitable combination of technical measures.
An example of technical measures that could be implemented in order to ensure rigorous containment is given in undermentioned example for workers and environmental protection in different industrial sectors. This example is in no way binding or exhaustive but illustrate the types of measures that can be applied.

Example Fine chemicals industry: examples of technical measures for workers and environmental protection.

Handling intermediates in batch fine chemicals facilities will require that the plant engineering and systems are designed to minimise potential for emissions to air and water. Typical examples of control measures and systems which might be encountered to deliver such strictly controlled conditions include:

- Material transfers via enclosed systems (e.g. semi-bulk containers such as IBCs)
- Enclosed and vented charging systems (e.g. bag slitters with integral package disposal)
- Discharging arrangements designed to minimise emissions (e.g. into drums/kegs via pneumatic filling heads and continuous liners; vented booths with exhaust scrubbing)
- Plant designed to facilitate the draining and flushing (and detoxification) of equipment items prior to maintenance
- Maximal use made of automated process control systems to minimise manual interventions
- Contained process sample systems (e.g. vented cabinets or sample bombs)

If the information available to determine whether the substance is rigorously contained during manufacture, use and handling, is not sufficient, then reliable model calculations and/or monitoring data could also be used to assess the exposure of workers or the environment to the substance. Product-based containment procedures depend on the form and use of the substance, e.g. some degree of containment is inherent in a liquid or a pasty substance with a very low vapour pressure or a solid that does not release dust in repacking/decanting or processing activities. Where a substance is in a matrix used for synthesis (e.g. masterbatch, glass, plastic), containment depends on the potential migration of the substance from the matrix.

10. Procedural and control technologies to minimise emission and any resulting exposure

Any significant release of the substance into the wider environment should be prevented through containment procedures, such as suitable physical barriers (e.g. bunds) and/or chemical barriers (e.g. membranes). Operations on site should be managed in order to ensure containment within the site premises wherever possible, including accident prevention, as specified under the section 13, “Management Systems”.
An additional way to minimise emissions and resulting exposure is to apply procedural and control technologies when emissions have been identified. Such technologies allow to still consider the substance to be rigorously contained. For example, in case of emissions to waste water (including during cleaning and maintenance processes), it will be considered that the substance is rigorously contained if the registrant can prove that techniques are used to minimise the emissions by, e.g. incinerating the waste water or extracting the intermediate from it. The same applies to emissions to air or disposal of wastes where procedural and control technologies are used to minimise potential exposure of humans and environment. The efficiency of any methods applied to minimise emissions and resulting exposure should be described and documented in-house. Furthermore the details of these methods (e.g. efficiency) must be included and described in the registration dossier. The documentation and description of methods applied can be based on the company's IPPC licence or permit, as long as sufficient and adequate documentation of the compliance with the conditions of the permit are available, and demonstrate rigorous containment of the substance. Following an assessment of containment, the selection and use of further risk management measures, equipment standards and safety procedures will vary considerably across industry and be dependent on the process and on the physico-chemical properties and the hazard of the substance, when sufficiently well known.

11. Handling of the substance by trained personnel

In order to minimise emissions and any resulting exposure, it is important that only trained and authorised personnel handle the substance (Article 18(4)(c). Procedures should apply to all personnel handling the substance including during cleaning and maintenance works. As a minimum, the registrant should take care that the workers who handle intermediates are provided with:

- training and information on appropriate precautions, working procedures during the malfunctioning of the process and in accidental situations, and actions to be taken in order to safeguard themselves and other workers at the workplace.
- access to a safety data sheet (SDS), which includes information on the hazardous properties of the substance, such as its identity, the risks to safety and health, relevant occupational exposure limit values (EU and national ones) and other relevant legislative provisions.

12. Cases of accident and when waste is generated

There must be procedural and/or control technologies in place that are used in cases of accidents and in cases when waste is generated (Article 18(4)(e)). In this, the clarifications according to Directive 96/82/EC on the control of major-accident hazards involving dangerous substances and Directive 94/9/EC concerning equipment and protective systems intended for use in potentially explosive atmospheres might usefully be consulted.

13. Management Systems

Management systems are good options to ensure the proper application of risk management measures. A management system should include the relevant operational procedures to ensure that control measures are indeed applied[6]. Such a system may also define management responsibilities, authorisation procedures (e.g. for maintenance or opening of equipment, inspection and auditing requirements etc). On any given site, a management system should contain reference to procedures for accident prevention and response. It may be appropriate to link this system to operational engineering control systems.
In case of a transported intermediate, the parties involved (supplier/customer) will need a management system to ensure rigorous containment and controlled conditions over the life cycle of the intermediate.

[6] In practice management systems include the structure to respond to accidents and demonstrate compliance with relevant occupational and environmental legislation and/or standards.

14. Registration requirements for transported isolated intermediates

Transported isolated intermediates have to be registered to the Agency if they are manufactured or imported in quantities of 1 tonne or more per year. In order to benefit from the reduced registration requirements for transported isolated intermediates, the manufacturer or importer must confirm himself or state that he has received confirmation from user(s) that the substance is used and manufactured only under strictly controlled conditions during its whole lifecycle as defined in *Article 18(4)* (see section 8, "Strictly controlled conditions").

Therefore the registrant of a transported intermediate should first get the necessary confirmation from the different users to whom the substance is supplied whether the substance is used under strictly controlled conditions or not.

For transported isolated intermediates below 1000 t/a, the information required under *Article 18(2)* is the following:

* **The identity of the manufacturer or importer**: the information to be submitted is detailed in section 8.2.2.3 of ECHA's Guidance on registration.
* **The identity of the intermediate**: the information to be submitted to identify the substance is the same as that to be submitted for a full registration (see section 8.2.2.3 of ECHA's Guidance on registration) with the exception of analytical methods descriptions (section 2.3.5 to 2.3.7 of Annex VI) which are not required.
* **The classification of the intermediate:** the registrant has to determine the classification of his substance with respect to physico-chemical properties, environment and human health. This classification has to be documented in section 2 of IUCLID 5, under the heading "classification". More guidance on classification and labelling is available in section 8.2.2.4 of ECHA's Guidance on registration.
* **Any available existing information on physicochemical, human health or environmental properties of the intermediate:** when the registrant is in legitimate possession or has the permission to refer to a full study report (a full study report or study summary can be used freely after at least 12 years after its submission in the framework of a registration (*Article 25(3)*), he shall submit a study summary within their registration). How to prepare a study summary is described in section 8.2.2.6 of ECHA's Guidance on registration.
* **A brief general description of the use:** only a brief general description of the identified use(s) of the substance as described in section 3.5 of Annex VI is required for isolated intermediates. More details can be found on what needs to be reported in section 8.2.2.5 of ECHA's Guidance on registration.
* **Details of the risk management measures applied and recommended to the user**: the details of the risk management measures should be reported in section 11 of IUCLID (Guidance on safe use), in particular in the fields "Handling and storage" and "Exposure controls/ personal protection". The information must include a description of the efficiency of the risk management measures applied, sufficient to demonstrate that the substance is manufactured and used under strictly controlled conditions and that it is rigorously contained during its whole lifecycle. Information on how to describe the risk management measures applied and their efficiency is available under ECHA's Guidance on the Chemical Safety Report.

For transported isolated intermediates in quantities of 1000 tonnes or more per year per manufacturer or importer the registrant shall include in addition information specified in Annex VII of the Regulation. More details can be found on what needs to be reported in ECHA's Guidance on registration.

From the available information and knowledge of the process on the different sites, or if no confirmation is available, the registrant may not be able to conclude that the substance is used under strictly controlled conditions. In that case, a full registration (including the complete set of information as requested for "standard" substances and described in ECHA's Guidance on registration) has to be submitted taking into account the manufactured or imported tonnage of the substance.

15. Preparation of a registration dossier for isolated intermediates

Article 111 requires that the format of the technical dossier must be IUCLID (International Uniform Chemical Information Database). Also other IT tools could be used to prepare the dossiers as long as they produce the exact same format. In this document only the preparation of registration dossier using IUCLID is described.
The last version of this software is IUCLID 5 for which a specific guidance is available (ECHA's *Guidance on IUCLID*). The IUCLID 5 software will be downloadable from the IUCLID website at http://iuclid.eu for free by all parties, if used for non-commercial purposes.
The full registration dossier should be submitted via REACH IT to the Agency as described in section 8.2 of ECHA's *Guidance on registration*.
For intermediates, IUCLID 5 enables the registrant to identify the information requirements for either on-site isolated intermediates, transported isolated intermediates produced at up to 1000 tonnes and transported isolated intermediates produced at 1000 tonnes or more per year. In each case, all available and relevant information need to be reported in the registration dossier. Depending on the selection of the registrant the fields to be filled in IUCLID 5 are clearly identified.

EXAMPLE OF FORMAT FOR DOCUMENTING IN-HOUSE INFORMATION ON STRICTLY CONTROLLED CONDITIONS OF ISOLATED INTERMEDIATES

This format can be used by

- *the registrant of an isolated intermediate (the manufacturer or importer) and*
- *the user of the intermediate wishing to confirm to the registrant that his use takes place under strictly controlled conditions*

1. Description of technological process used in manufacture

2. Description of the uses of the substance.

Give a description of the uses of the substance on the different sites.

Check that any relevant storage, processing and the synthesis process of the final substance have been accounted for.

3. Is the substance rigorously contained:
a. During the manufacturing process?

- Description of the process and technical means to contain the substance.
- Identification of potential emissions to:
- Workplace
- Environment
- Modelling estimations or available monitoring data if needed
- Procedure and systems in place to comply with existing health, safety and environmental legislation.

b. During the use?

- Description of the process and technical means to contain the substance.
- Identification of potential emissions to:
- Workplace
- Environment (air, wastewater, soil, etc.)
- Modelling estimations or available monitoring data if needed.

4. If emissions have been identified on sites of manufacture or uses, are there procedural and control technologies to minimise emission and resulting exposure?
Give a description of these procedural and control technologies in place.

5. Is the substance handled by trained and authorised personnel?

- Is the personnel provided with safety data sheet (SDS) of the substances handled?
- Is there sufficient training and information on appropriate precautions and working procedures (proper labelling of specific working places) at workplace?
  Give a description of the information and training in place.

APPENDIX 4: PROCESSCHEME CHEMICAL RISK ASSESSMENT UNDER REACH

APPENDIX 5: DANGEROUS RAW MATERIALS AT THE SITE ANFCH

RAW MATERIAL	CAS.NR.	UN NR.	GEVI NR.	CHEMICAL CHART	CLASSIFICATION	FLASH POINT	R-PHRASES
AMMONIA 25%	1336-21-6	2672	80	78	Corrosive, C Dangerous for the environment, N	n.a.	R34-50
DIETHYLENETRIAMINE	111-40-0	2079	80	102	Corrosive, C	102 ^{O}C	R21/22-34-43
ETHYLENEDIAMINE (EDA)	107-15-3	1604	83	167	Corrosive, C	34 ^{O}C	R10-21/22-34-42/43
AMINOETHANOLAMINE (HEDA)	111-41-1	2735	80	740	Corrosive, C Toxic, T (Reprotoxic)	130 ^{O}C	R61-62-34-43-52/53
FORMALIN 44%	50-00-0	2209	80	21	Toxic, T	60 ^{O}C	R23/24/25-34-40-43
SODIUMCYANIDE 30%	143-33-9	3414	66	789	Very toxic, T^{+}, Dangerous for the environment, N	n.a.	R26/27/28-32-50/53
NITRILOTRIACETONITRILE (NTAN)	7327-60-8	2811	80	n.a.	Irritant, X_i Toxic, T	n.a.	R25-41
1,3 PROPYLENEDIAMINE TETRAACETONITRILE (PDTN)	110057-45-9	n.a.	n.a.	n.a.	Dangerous for the environment, N	n.a.	R52/53
ETHYLENEDIAMINE TETRAACETONITRILE (EDTN)	5766-67-6	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

APPENDIX 6: MEASURES IN CASE OF AN EMERGENCY

Because of the hazardous properties of (some) chemical products it is important that attention is given to safety and risk reduction by ensuring that emissions are maintained as low as reasonably practicable. For this reason good engineering practices, safe working conditions and safe working practices have been developed on an industry basis.
Within ANFCH, these are incorporated in Standard Operation Procedures (SOP) which are continuously and strictly used during normal operations in the production, the logistics and the maintenance department. In case of an emergency, the Site Emergency Plan will become effective and safety workers, well equipped with sufficient & appropriate PPE (and if necessary compressed air), will control the emergency. If needed governmental emergency services, like the fire fighting brigade, should be called for assistance.
In the following a brief overview is given of a main part of the Site Emergency Plan within ANFCH.

SITE EMERGENCY PLAN

Attachments:

. Tasks and Features.
. Important phone numbers.
. Contacts in accommodation centers.
. Scenarios in the context of Safety.
. Decision scheme of alerts going out to the security room.
. Suppress incidents.
. Education and training of CEA 2009
. Test and training of the Site Emergency Plan .
. How to act in case of fire.
. How to act in case of an accident.
. How to act in case of any disturbances.
. Questionnaire incoming emergency report.
. Questionnaire emergency report to security room.
. Questionnaire subversive action.
. Instructions attn. spilled chemicals (3 pages).
. Instruction in respect of kegs Paraffin oil.
. Emergency power supply.
. Map of fire extinguish management. (only in hard copy)
. Bill of Materials + map of buildings, tanks, shelters, etc. (only in hard copy)
. Chemical cards.
. List of hazardous substances.

N.B.: The SITE EMERGENCY PLAN itself is a checked document, the annexes, however are not. This implies that until further notice the necessary, operational emergency plan will regularly be replaced entirely by a new version.

FOREWORD.

Despite all the safety and security regulations, emergencies (incidents) can not be excluded.

There is an emergency when, due to an accident, fire or leakage of toxic and/or inflammable liquids and/or fumes, there is a threat formed to people and/or facilities, inside the factory, at the site, or in the immediate surroundings of the site.

This **SITE EMERGENCY PLAN** has been created, so everyone knows what to do in case of an emergency.

Whether there is an actual emergency situation, this is determined by the COMMAND TEAM.
In case of an actual emergency the alarm must be activated.

The site emergency plan is a **Confidential** business document specific to the local situation.
It includes a description of the organizational structure, the responsibilities, communication, emergency procedures and adjusting with external rescue services of the site in case of an emergency.

To make sure that all the above mentioned procedures (rules, responsibilities and communication) are kept up to date, the site emergency plan must at least be updated, annually. Unless it is determined that there is no need to do so. Everyone should be able to use the site emergency plan immediately.

The Safety Report of Akzo Nobel Functional Chemicals B.V.is the foundation for this site emergeny plan. The scenarios mentioned are entirely based on those included to the Safety Report.

The site emergency plan and the Safety Report are in agreement with eachother and are in line of eachother.
For a more complete description of these scenarios, one is referred to the Safety Report.
An enumeration with clarification has been added in the annexes.

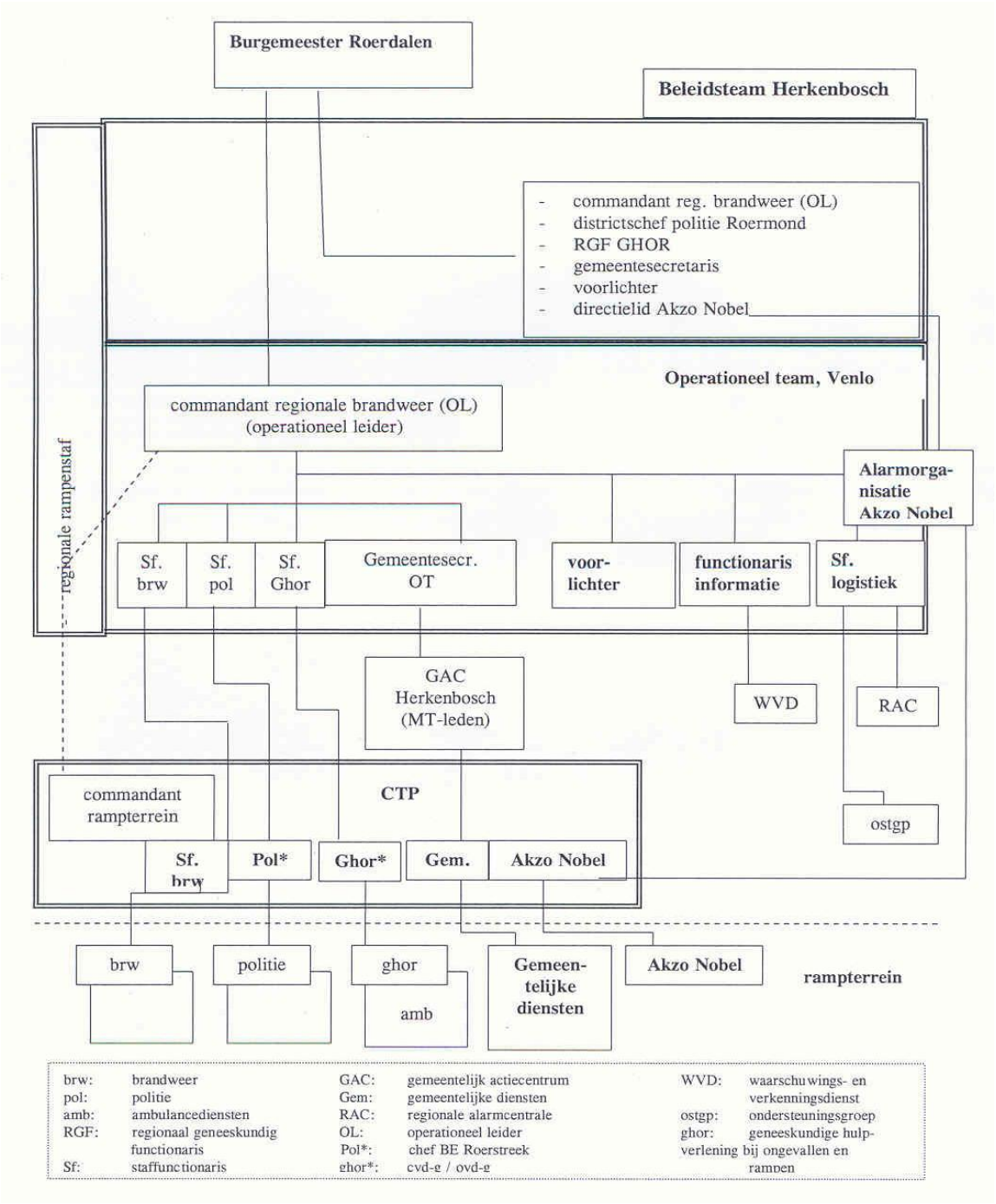
2. **SENDING LIST SITE EMERGENCY PLAN.**

2.1. SECRETARY SITE EMERGENCY PLAN	1 x
2.2. COMMAND TEAM & SITE MANAGER	16 x
2.3. RECEPTION / TELEPHONE	1 x
2.4. MUNICIPALITY ROERDALEN	3 x
2.5. FIRE BRIGADE MUNICIPALITY ROERMOND	2 x
2.6. DOCTORS NAUS / MANNENS (each 1 x)	2 x
2.7. ARBONED South-East Netherlands	1 x
2.8. OFFICE PRODUCTION CHEFS	1 x
2.9. OPERATINGROOMS (each 1x) (Reaction factory; Metalchelats, Derivats factory; Mother liquid Digestion; Aromox / Nozzle dryers; PPK / IWA / MPU; MPA; CPU)	8 x
2.10. LABORATORY	1 x
2.11. TECHNICAL DEPARTMENT (Work preparation)	1 x
2.12. LOGISTICS ("HOUSE No. 5160")	1 x
2.13. WORKS COUNCIL	1 x
2.14. CRISIS CENTRES	6 x

3. ORGANIZATION.

3.1. Overall.

In case of an emergency, another organizational plan becomes effective. This differs from the standard situation. Depending on the type and level of alarm (*see Chapter 4*), the following organizational structure shall entirely or partially become effective.



Both management of Akzo Nobel Functional Chemicals B.V.and government have, in case of an emergency, a responsibility for suppressing the emergency itself as well as limiting the consequences of the emergency, both at the location itself and in the surrounding areas.

The site manager takes, on behalf of the location, place in the policy team.
The tasks of the policy team and the operational team are described in the contingency plan for the site of the municipality Roerdalen.
The composition and functions of the command team of Akzo Nobel Functional Chemicals B.V. are described in Chapter 3.2 and 3.3 of this SITE EMERGENCY PLAN.
Akzo Nobel Functional Chemicals B.V.decides, beforehand, which alarm phase is relevant for the emergency and which level of external aid should be involved (see Chapter 4).

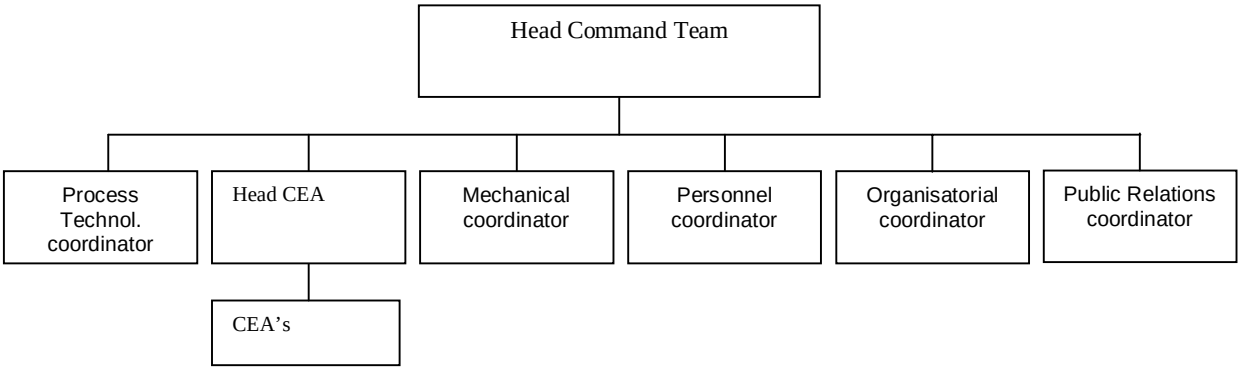
To prevend loss of time, with every serious alarm it is assumed that there is an emergency situation. Therefore, any serious internal alarm notification of any size is followed by an external reporting. If in a later stage it appears to be that this is unnecessary, there will still be a few things corrected (see Chapter 4).

3.2. COMMAND TEAM.

3.2.1. Purpose and organization

The main role of the **"COMMAND TEAM"** is, in case of an emergency situation, manage people and processes, so emergency situations can be suppressed in the best possible way.
The command team consists of 14 expert officials, seven of whom have a chemical-technical background and 7 who have a more organizational background.
The following disciplines are part of the command team: Head Command Team, Head CEA organization, Process Technology Coordinator, Mechanical Coordinator, Personnel Coordinator, Organizational and Press Coordinator.

Figure 0-1: Emergency Suppress Organization



3.2.2. Functions and authority of the members of the COMMAND TEAM.

The **Head Command Team** coordinates during emergency situations the implementation of the various tasks, provides for the "Briefing" and maintains contact with government incl. the municipality, police and labour inspection and officials within Akzo Nobel.

The **Head of the CEA-organization** is responsible for suppressing the incident and maintains contact with the fire brigade. He is also charged with environmental and safety issues.

The **Process Technology Coordinator** is charged with the (secure) decommissioning of the production units, is responsible for internal transportation during an emergency and charged with ensuring the stored raw materials and finished products.

The **Mechanical Coordinator** attends to the utilities, such as: gas, steam, electricity & (fire-fighting-) water and provides "technical assistance" and tracks the "logbook".

The **Personnel Coordinator** maintains contact with the doctor(s), the hospital and the Labor Safety Advisor as well as relatives of possible victims and the "home front" of the remaining employees and also helps the telephone-service.

The **Organizational Coordinator** is responsible for evacuation of personnel to the crisis centers. He also checks who, of personnel being present at the site at the time of an emergency (including those of third parties). He uses the attendance system which is used at the site. He also takes care of the tracking of the "logbook".

The **Press Advisor** is responsible for maintaining contact with the press and the other, not yet mentioned external communication. Besides that, he also answers the telephone.

All members of the command team are authorized to take necessary decisions,in capacity of their profession. If there is any doubt, the head of the command team decides.
All tasks of the members of the command team may be executed by the location manager; who is overall authorized to take decisions.

3.2.3. Replacement, Consignment and Attendance.

For the members of the COMMAND TEAM there is a replacement and a consignment scheme drawn up (see appendices).
From each group 1 person is, by rotation, the consignee.

The members of the COMMAND TEAM are (automatically) called through ***987*** or by manually calling on the mobile phone number of the consignment system (see below overview "tasks and functions").
The attendance time for members of the COMMAND TEAM is, during office hours, put on "immediately call to" and the consignee members after office hours to 30 minutes.

3.3. Company Emergency Assistant (CEA's).

3.3.1 The aim of the CEA organization.

The purpose of the CEA organization is "providing assistance and preventing expansion of emergencies". Specifically, this concerns:

* Providing first aid to casualties (perform life-saving operations and transport of wounded);
* Restrict and suppress fire and other emergencies, moreover, preventing and reducing accidents without undue risk to the CEA;
* Alerting and evacuating all employees, contractors and visitors;
* Attend to and cooperate with the fire department / other rescue organizations.

3.3.2. Organization, tasks, responsibilities and attendance

The CEA organization operates under the responsibility of the Command Team and follows orders. The head of the CEA organization is the HSE manager.
After office hours, one of the on-duty production team leaders observes.
Tasks: achieving the CEA-objectives in the event of an emergency.
Responsibilities: carry out the CEA-tasks within the CEA organization.
Turnout: CEA's are summoned through **987**.
The attendance time is: "Immediately at call".

3.3.3. Requirements of the CEA's.

CEA's should be adequately trained and qualified.
A training in the field of respiratory, small extinguishing tools, other repression tools, life-saving operations and transport of wounded is often necessary.
The nature of the training should reflect the specific company situation. Therefore, in our case, because of the use of cyanide, this training package for a significant part of the group CEA's is extended with resuscitation / cyanide training.

Besides gaining knowledge and improving skills, the need to maintain the right level is kept by practical lessons and exercises which are repeatedly frequently (see training and training CEA 2004).
Given the nature of the possible functions of the CEA's there is a regular medical inspection required and the maximum age limit for participation is set at 55 years.

3.3.4. Equipment of CEA's *).

To perform their functions properly, the CEA's have at their disposal:

- Means of communication: pager (call through **987**), portable radio and portable phone.
- Combating tools: fire fighting water from the fire fighter water network (11 hydrants, each with its fire hose cabinet), a stationary foam extinguisher for the bulk liquid storage of raw materials in the Reaction Factory (cap. 45 min. foam), hand extinguish devices (about 90 pieces, divided over the location), foam extinguishers (5 pieces, 1 in every Logistics hangar), risella oil (1 barrel to 4,000 l. The ammonia storage, 2 barrels to 230 & 850 liters in the hydrochloric acid storage).
- Protective Equipment: respiratory protective equipment (6 pieces regularly divided over the location), personal protective equipment (gas mask, [chemical proof] gloves) & protective clothing (safety footwear, fire safety jacket).
- Medical devices: first aid room (+ belongings in Personnel Building No 5191), 4-DMAP (3 boxes with injections, at the relevant sites), oxygen cases (5 pieces,
  on the relevant sites), bandage boxes (14 pieces regularly divided over the location).
- Technical devices: (in principle all present at the site technical devices)

3.3.5. Other emergency services.

Depending on the alarm phase during an emergency situation, external rescue services such as the regional fire fighting department and the ambulance service are summoned. The commitment of these rescue services is described in the emergency suppression plan of the municipality Roerdalen.
*) CEA's, trained for the course "4-DMAP & resuscitation", will also be trained in the operation of a defibrillator.

4. HOW TO ACT IN CASE OF INCIDENTS AND/OR EMERGENCIES / IN AN EMERGENCY.

4.1. Description of incidents and related reports.

"Incidents", *unusual occurrences with (potential) adverse effects on the environment or working conditions*, should be accurately reported as "emergencies". The nature of these emergency alerts vary from case to case (from "immediately" to "within 10 days"). Defendable is a deadline so short that the situation itself still can be reviewed, e.g. immediately after or during the handling of the incident.

Note: ALERTS MUST BE CONFIRMED WITHIN 15 MIN. BY FAX OR EMAIL.

The accomplishment has been delegated to the HSE manager. However, if he is not present or by capacity of his position (head CEA) in charge of suppressing the incident. To ensure that incidents still are alerted "flawlessly", agreements are made regarding the accessibility of the government. It's about the following incidents and report procedures:

- Incidents with environmental impact or with potential effects outside the site or where BRZO chemicals are involved.

Reporting to the Municipality Roerdalen, city hall St. Odiliënberg + reporting room of the fire fighting brigade. (empathizing on incidents involving potential effects outside the location where BRZO chemicals are involved)

* During office hours: 0475 - 538136 or 06-53198279 (Hr. M. van Bommel) - fax: 0475 - 538899 0475 - 538,131 (Mrs. C. Ernes) or 0475 - 538138 or 06-51647611 (Hr. Heijnen)
* After office hours: 043 - 3617070 (Provincial Environment Complain Line, which warns the picket service)
* 24 - 7: 077 - 3565656 (Reporting room of the Fire brigade, reporting of non urgent cases)
  Indicate that it concerns an incident at Akzo Nobel Functional Chemicals B.V.Herkenbosch, with a brief description of the nature of and extent of the incident and any foreseenable effects on the environment and surroundings. Depending on the situation the fire brigade will turn out or it remains standby at the barracks and will wait for further messages, in deliberation with ANFCH. If the phone at the municipality, in daytime, is answered by the operator / receptionist, then, because of the incident, ask strongly for the appropriate municipal official.

Note: The Municipality / Province uses for our type of company the term "BRZO company".

- Incidents where there is an excess of the discharge standards from our WVO license and / or discharges of pollutants (under which BRZO Chemicals) with an adverse impact on surface and / or the proper functioning of the sewage water treatment in Roermond.

Reporting to the District Water Board Company Limburg (DWBCL), Office Roermond fax: 0475 - 311605

* During office hours: 046 - 4205832 (Hr. P. Gubbels)
* After office hours: 0800 - 0341 (Dirty Water Watch, and may warn DWBCL-picket service)
  Indicate that it concerns an incident at Akzo Nobel Functional Chemicals B.V.Herkenbosch, with a brief description of the nature of and extent of the incident and any likely impact on surface water or the proper functioning of the water refinery in Roermond. If the phone at the DWBCL is answered, in daytime, by the operator / receptionist / departmental secretary, ask, because of the incident, strongly for the appropriate official.

- Incidents involving a labor accident with serious physical or mental injury and / or hospital recording or at which BRZO chemicals are involved.

Reporting to the Labour Inspection, Office Roermond fax: 0475 - 356660

* During office hours: 0475 - 356666, ask for Mr. M. de Haan
* After office hours: 0475 - 356666, insert incident reporting in an answering device

Indicate in the report that it concerns an incident at Akzo Nobel Functional Chemicals B.V.Herkenbosch, including a brief description of the nature of and extent of the incident.
If, during daytime, the phone is answered by an operator / receptionist or the departmental secretary, ask, because of the incident, strongly for the appropriate official.Note: The Labour Inspection uses, for our type of company, the term "Major Hazard Company".

- ***Transportation incidents (see ADR 1.8.5)***

Notifications (see ADR 1.8.5, within 10 days) through the standard form (see ADR 1.8.5.4):
The Minister of Transport and Water Management, through
the Advisory Traffic and Transportation, PO Box 2510, 6410 DA Heerlen, fax 045 - 5605209.

APPENDIX 7: SOME USEFUL AND ENVIRONMENTAL ASPECTS OF THE DISSOLVINE®CHELATES

More details regarding some of the very useful properties of the Dissolvine® chelates and their mild environmental profile, including a lot of literature references, are given in this Appendix. This is done by means of 3 papers, dealing with the biodegradation of EDTA, the risk characterization regulation of chemicals in the USA and the useful properties of Ferrazone®.

BIODEGRADATION OF EDTA

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Abstract
In this paper important aspects of the biodegradation of Ethylenediaminetetraacetic acid (EDTA) are discussed; namely the mechanism of biodegradation, the influence of the counterions, biodegradation in officially recognised OECD tests and biodegradation in wastewater treatment plants and ecosystems.
EDTA is cleaved into ethylenediaminetriacetate (ED3A) and glyoxylate. ED3A is then metabolised via N,N'-ethylenediaminediacetate or alternatively through a cleavage into iminodiacetate and iminoacetaldehydeacetate. All intermediates formed are readily converted into biomass, water, carbon dioxide and ammonia. The chemical speciation of organic compounds including EDTA influences the mineralisation. For instance micro-organisms decompose calcium magnesium and manganese complexes of EDTA but not Fe(III)EDTA.
EDTA has been classified as a recalcitrant compound due to results obtained in early biodegradability tests. In these biodegradability tests, less than 20% of the initial theoretical oxygen demand or theoretical organic carbon was degraded. Recently, surface waters and activated sludge were tested and EDTA-degrading micro-organisms were found in all of these probes after prolonged incubation periods in Closed Bottle tests.
Under alkaline conditions ready biodegradation of EDTA was observed in screening tests, inherent biodegradability tests and simulation tests of activated sludge plants. These tests indicate that it is rather easy to establish an activated sludge treatment capable of removing EDTA. Indeed, several full-scale systems remove EDTA if the sludge age is high enough to ensure that the competent micro-organisms do not wash out.
Based on biodegradation mechanisms, OECD tests and results in full-scale treatment plants, it was concluded that EDTA is inherently biodegradable and that the biodegradation process results in complete mineralisation.

Introduction

EDTA has numerous applications, based on its ability to control the action of different metal ions. Pulp and Paper and Industrial and Institutional (I&I) cleaning are the most important application areas. In cleaners for industrial use, EDTA prevents precipitation of calcium and magnesium, which cause deposits and crusts.
In all steps of pulp and paper processing the presence of metal ions causes difficulties which can be eliminated by addition of EDTA. Because EDTA is water-soluble, it is released mainly with industrial effluents after use.
This widespread use of EDTA has raised concern over and interest in the fate of this water-soluble compound. At present, EDTA is often considered recalcitrant and classified as nonbiodegradable.
The objectives of this paper were to review biodegradability test results of EDTA and to verify through metabolic studies that this compound undergoes complete biodegradation. Finally, the behaviour of EDTA in full-scale treatment plants is discussed including unpublished Akzo Nobel results

Studies with micro-organisms

Enrichment cultures and EDTA-utilising isolates

The first evidence of EDTA biodegradation was found by Tiedje (1975) and Belly *et al* (1975). EDTA degradation was detected in mixed cultures grown on easily biodegradable compounds. During growth on these compounds certain micro-organisms expressed non-specific enzymes that also catalyse transformation of EDTA. This transformation is termed cometabolism. The absence of successful enrichments with EDTA as sole carbon and energy source also suggested that EDTA was cometabolically transformed (Tiedje, 1975).
More recently, however, growth-linked biodegradation was established as well. Fe(III)EDTA supported growth of the *Agrobacterium sp* (Lauff *et al,* 1990). Nörtemann (1992) also obtained a pure culture (strain BNC1) which could quantitatively utilise EDTA as a sole source of carbon and energy for growth. In contrast to the *Agrobacterium sp,* strain BNC1 preferred other metal chelates. Fe(III) was not metabolised by strain BNC1.
Furthermore, growth of micro-organisms utilising EDTA as sole source of energy was observed in a continuously fed bioreactor maintained at a pH of >9 (Gschwind, 1992). In this reactor EDTA-utilising micro-organisms were attached to a carrier. Starting from this enrichment culture Witschel *et al* (1997) isolated a gram-negative strain DSM 9103 capable of degrading EDTA. EDTA can serve as a carbon and energy source for strain DSM 9103 under neutral conditions. Finally, EDTA-utilising enrichment cultures were obtained from river sediment and activated sludge from a plant treating domestic wastewater (van Ginkel *et al,* 1997a; Russell *et al,* 1998).
In summary, it is possible to obtain enrichment cultures of EDTA-utilising micro-organisms and three bacteria have been isolated that can break down EDTA completely. These include an *Agrobacterium* and two unidentified strains.

Metabolic pathway
The use of pure cultures of micro-organisms is a valuable tool in elucidating the metabolic pathway of degradation of EDTA. Two pure cultures of micro-organisms capable of degrading EDTA have been studied (Klüner *et al,* 1998; Witschel *et al,* 1997; Payne *et al*, 1998). Two metabolic pathways have been suggested by which these micro-organisms degrade EDTA. The proposed pathways are detailed in Fig 1. One proposed pathway is associated with a gram-negative isolate (DSM 9103) (Witschel *et al,* 1997). This degradative pathway is similar to a pathway suggested to be present in BNC1 (Klüner *et al,* 1998). In both cases EDTA is degraded through ethylenediaminetriacetic acid (ED3A), *N,N'*-ethylenediaminediacetic acid (*N,N'*-EDDA) and glyoxylic acid.
The enzyme responsible for the key cleavage step is known by the name of EDTA monooxygenase because molecular oxygen, NADH and FMN are required as cofactors. The enzyme catalyses hydroxylation of the α carbon of a carboxymethyl group. EDTA monooxygenase also catalyses the removal of a second carboxymethyl group. This reaction is stereoselective because only *N,N'*-EDDA was detected as a product of EDTA monooxygenase (Witschel *et al,* 1997). Cell-free extract of the EDTA grown bacterium (DSM 9103) converted *N,N'*-EDDA without the addition of any cofactors. The enzyme concerned has not been purified, nor have studies been carried out to elucidate *N,N'*-EDDA metabolism.
Simultaneous adaptation studies with washed whole-cell suspensions of BNC1 provided insight into a second pathway. Strain BNC1 grew on EDTA, ED3A, nitrilotriacetic acid (NTA), iminodiacetic acid (IDA), glycine and glyoxylate. EDTA grown cells were found capable of immediate oxidation of ED3A, IDA, glycine and glyoxylate. Strain BNC1 did not oxidise *N,N'*-EDDA and *N,N*-EDDA (Klüner *et al,* 1998). It is presumed that α-hydroxylation of EDTA by a monooxygenase present in the EDTA degrading bacterium BNC1 also forms a short-lived intermediate which undergoes aqueous hydrolysis to produce glyoxylic acid and ED3A. ED3A is transformed by removal of another carboxymethyl group by another monooxygenase or, alternatively, ED3A may be converted into IDA and iminoacetaldehydeacetate (Fig 1).
In summary, EDTA is degraded in bacteria by two pathways both of which lead to breaking of the carbon-nitrogen bonds. In the first pathway, cleavages of the carbon-nitrogen bonds result in stepwise removal of carboxymethyl groups. EDTA is converted into ED3A, which is further cleaved into IDA and iminoacetaldehydeacetate in the second pathway. These results illustrate that EDTA is completely mineralised by micororganisms.

Influence of counterions on EDTA degradation
Because EDTA is a charged molecule, it is associated in solutions with counterions. Counterions exert an effect on the biodegradation of chelating agents such as citric acid and nitrilotriacetic acid (NTA) (Brynhildsen and Rosswall, 1989; Firestone and Tiedje, 1975). Since stability constants of metal-EDTA complexes usually exceed those of the other chelating agents by some orders of magnitude, a greater effect of counterions on EDTA biodegradability is expected.
The effect of counterions on the decomposition of EDTA by strain BNC1 was extensively studied by monitoring the degradation of EDTA by whole cells and cell-free extracts (Klüner *et al*, 1998). In general, metal-EDTA complexes with a thermodynamic stability below 1012, like Ca, Mg and Mn, were readily mineralised. Chelates with a stability constant greater than 1012, such as Cu and Fe, were not degraded by strain BNC1. The activities of whole cells and cell-free extracts differ. This suggests that biodegradation of some metal complexes is limited by the rate of transport extracts (Klüner *et al*, 1998).
EDTA-utilising activated sludge was shown to degrade Ca, Mg and Mn chelates of EDTA. Fe(III)EDTA, however, was not degraded by activated sludge. The high proportion of Fe(III)EDTA in wastewater of several pulp and paper mills strongly indicates that Fe(III)EDTA complexes may be the cause of decreased biodegradation by activated sludge in full-scale plants investigated (van Ginkel *et al,* 1997b ; van Ginkel *et al,* 1999).
Non-biodegradability of some EDTA complexes may be overcome by addition of inorganic phosphates in the wastewater as a precipitant or displacement of Fe(III) by Ca at increased pH (van Ginkel *et al,* 1997a; Russell *et al*, 1998). Further studies of how metal complexes influence biodegradation of EDTA in treatment plants and natural ecosystems are needed.

Biodegradability testing

Ready-biodegradability tests
Closed Bottle tests, MITI tests and Sturm tests are known as ready-biodegradability or screening tests. In these tests the biodegradability of organic compounds is determined by measuring the oxygen consumption or the production of carbon dioxide. Biodegradation in the ready-biodegradability tests is expressed as the ratio of oxygen uptake or carbon dioxide production to the theoretical oxygen demand or theoretical carbon dioxide production. Therefore, a result of one hundred per cent biodegradation is impossible because part of the organic carbon is used for the formation of biomass. Experience demonstrates that in a screening test a biodegradation percentage of over 60 may be consistent with the complete or ultimate degradation of the organic compound.
In ready-biodegradability tests, EDTA generally displays low levels of biodegradation. For instance, with preacclimatization of the inoculum only 10% carbon dioxide evolution was observed in a 28-day Sturm test (Gerike and Fischer 1979). In Closed Bottle tests the oxygen consumption at day 28 was 3 and 0% of the theoretical biological oxygen demand as found by Gerike and Fischer (1979) and van Ginkel and Stroo (1992), respectively. However, recent data suggest that in ready-biodegradability tests EDTA is degraded especially under alkaline conditions (van Ginkel *et al*, 1997a). Various environmental samples were therefore monitored in the Closed Bottle test for their potential to degrade EDTA over a few weeks at pH 6.5 and 8.0. To this end, the Closed Bottle tests were inoculated with water from a river, a ditch and a lake. The ditch water sample was collected near Zevenaar,

the Netherlands, and the river water sample was obtained from the river IJssel near Arnhem, the Netherlands. The lake water was taken from Ketelmeer, a shallow freshwater lake situated in the central part of the Netherlands. The results of the Closed Bottle tests are shown in Figures 2 to 4 (unpublished Akzo Nobel results). The degrees of biodegradation observed at the last days of the Closed Bottle tests ranged from 60 to 89%. The biodegradation percentages achieved in these oxygen consumption tests strongly indicate that EDTA is completely biodegradable. At pH 8, the lag period for the onset of EDTA degradation was approximately four weeks, and at pH 6.5, approximately six. These Closed Bottle test results were also used as a basis for the estimation of half-lives, using only data from the logarithmic part of the curve. Half-lives for EDTA ranged from 2.3 to 4.3 days, the half-lives at pH 8.0 being lower. From these results, it is evident that acclimatisation and biodegradation of EDTA occurs in natural waters. Results obtained in ready-biodegradability tests at slightly alkaline conditions are environmentally relevant because the actual pH values of the lake and river water ranged from 7.7 to 8.5. The most surprising finding is the biodegradation of EDTA at pH 6.5 in the prolonged Closed Bottle tests. Hitherto, biodegradation of EDTA was not observed in the Closed Bottle test at neutral conditions inoculated with micro-organisms derived from activated sludge plants. The discrepancy between the recent results and older data from literature may be caused by an evolutionary adaptation process.

Inherent biodegradability tests

Activated sludge in a semicontinuous activated sludge (SCAS) test operated at neutral conditions failed to degrade EDTA (Fig. 5), even after an incubation of 6 months. In contrast, extensive removal of EDTA was achieved with SCAS units fed with 65 mg/L EDTA operated at pH values from 8.0 to 9.0. After an acclimatisation period of four weeks, up to 100% of the EDTA carbon was removed in the SCAS unit. Concurrently with the removal of EDTA, additional formation of 5.6 mg/L NO3-N was detected. The mass balance on nitrogen shows a discrepancy of approximately 10% between the theoretical and measured values, with the theoretical formation of nitrate being higher than that measured. The discrepancy is attributed to the use of nitrogen for the synthesis of biomass. The formation of nitrate in the SCAS unit fed with EDTA is additional evidence of the mineralisation of EDTA. As activated sludge is not deliberately discarded in the SCAS test performed in accordance with the OECD Guidelines, very high sludge retention times (SRTs) are maintained. To investigate the effect of SRTs on removal efficiency, various amounts of sludge were removed from the units (van Ginkel *et al*, 1997a). EDTA removal percentages in excess of 90 were consistently achieved for SRTs ≥ 12 days. In the units maintained at SRT ≥ 12 days, the nitrate levels increased compared to the unit maintained at an SRT of 6 days. The release of nitrate into the solution coincided with EDTA consumption (van Ginkel *et al*, 1997a).

Simulation tests

EDTA removal was not observed in CAS tests fed with domestic wastewater spiked with EDTA (Gerike and Fischer 1979). This result probably simulates the behaviour of EDTA present in domestic wastewater in activated sludge plants. The treatability of wastewater from two pulp and paper plants was tested in CAS tests (van Ginkel *et al,* 1999*)*. In these CAS studies the biodegradation of EDTA was assessed by means of HPLC and NPOC analyses. EDTA was present in wastewater from a pulp mill at a concentration of 10 mg/L. No degradation was detected at neutral conditions. Under alkaline conditions extensive removal of EDTA was achieved (van Ginkel *et al,* 1999*).* The biodegradation of EDTA in the CAS units was always accompanied by nitrate formation in the effluent. Microbial attack of EDTA in pulp and paper wastewater was detected by Ek *et al* (1999) in a laboratory study. In this study biodegradation was observed at pH 7. However, the degradation EDTA proceeded much faster at a pH of 8.5. The treatability of wastewater of a dairy plant was studied in a CAS unit maintained at an SRT of 20 days and a hydraulic retention time of 1 day. An alkaline pH was achieved in the CAS unit fed with only wastewater from a dairy plant without any additional measures. The EDTA of the wastewater flowing into the unit was approximately 30 mg/L, whereas the steady-state effluent concentration from the unit was between 0.5 and 1.5 mg/L (unpublished Akzo Nobel result). The residual EDTA was therefore less than 5% of the initial EDTA level. The biodegradation of EDTA in the CAS units was accompanied by nitrate formation in the effluent. EDTA-nitrogen was almost completely recovered as nitrate, demonstrating that EDTA is completely biodegraded.

Fate in full-scale biological wastewater treatment systems

Activated sludge systems are principally designed to remove organic compounds present in domestic and industrial effluents. At present, the general consensus is that EDTA is not removed from waste water in biological treatment systems. Since EDTA is highly water-soluble, removal by adsorption or precipitation during biological treatment is unlikely. This is confirmed by Gardiner (1976), who reported negligible adsorption of EDTA on suspended solids. EDTA degradation in existing conventional activated sludge plants designed for treatment of domestic wastewater was monitored at several full-scale plants (Gardiner, 1976: Alder *et al,* 1990; Kari and Giger, 1996*)*. These monitoring studies confirm the general consensus because no removal was detected in these activated sludge treatment plants. However, recently Nirel *et al* (1998) observed significant removal of EDTA in three of five plants treating domestic wastewater. Although Nirel *et al* (1998) atttribute the removal to photodegradation, biodegradation of EDTA should not be excluded in view of the findings described in this paper. In laboratory biological treatment systems enhanced degradation of EDTA by immobilised micro-organisms was observed at pH > 9 (Gschwind, 1992). EDTA in domestic wastewater was successfully degraded by activated sludge in SCAS reactors operated under slightly alkaline conditions at sludge retention times ≥ 12 days *(*van Ginkel *et al,* 1997).

Full-scale studies should provide the necessary real-world confirmation of the laboratory results by giving special attention to the SRT and the pH. Five activated sludge plants treating wastewater from Industrial and Institutional (I&I) cleaning, including public and private treatment systems, were evaluated (Table 1). These facilities only or predominantly treat wastewater from the dairy, soft drink, and beer industries. The influent samples were taken from the discharge of the industrial plants or the primary clarifier of the activated sludge system. The effluent samples were taken from the discharge of the secondary clarifier. Excellent performance was obtained from plant I, with effluent EDTA concentrations in the 2 to 8 mg/L range. The pH in the activated sludge treatment system was slightly alkaline due to the use of NaOH during Cleaning In Place (CIP). The SRT calculated in Plant I was approximately 20 days (van Ginkel *et al,* 1997). This SRT enables EDTA-degrading micro-organisms to maintain themselves in the activated sludge system. Effluent from another plant (II) was biodegraded by activated sludge, with over 90% reduction in the COD and only 50% removal of EDTA. The microbial degradation of EDTA containing wastewater from this dairy plant is thus only partially successful. The pH values measured ranged from 7.3 to 7.7, which is no optimal condition for biodegradation of EDTA. The activated sludge of plant III was capable of removing 30 % of the EDTA. The partial removal can probably be attributed to an SRT of approximately 9 days in the activated sludge system. The pH in this activated sludge plant was within the optimal range.
Plant IV experienced two seasonal changes characterised by a cold winter (5°C) and a summer (20°C) during the monitoring study. The SRT of this plant was approximately 40 days and the pH measured ranged from 7.5 to 8.0. In the summer, the removal of EDTA was 95%. However, in the winter, the extent of elimination of EDTA was only 35**%.** At 5°C, an SRT of approximately 40 days probably still results in a wash-out of the competent EDTA-utilising micro-organisms.
A comparable well-known phenomenon is the low conversion of ammonium into nitrate by activated sludge at low temperatures due to wash-out of nitrifying bacteria. The wastewater studied, i.e. from dairy, soft drink, and beer plants, were alkaline. This is also true for the wastewater from plant V. In contrast to the other plants investigated, wastewater of plant V was neutralised before being discharged into a public activated sludge plant. Under the neutral conditions achieved no EDTA removal was detected in the activated sludge system. A laboratory-scale CAS system maintained at pH 8 effectively reduced the COD of the wastewater, at the same time transforming the EDTA nitrogen into nitrate. An EDTA removal percentage of ≥ 95 was accomplished in a CAS unit (see above). Up to now no reduction of EDTA in pulp and paper mill wastewater was observed in activated sludge plants operating under neutral and acidic conditions *(*Saunamäki, 1995*)*. In contrast, the results obtained in laboratoryscale experiments indicate that up to 95% of EDTA can be degraded if the pH level is raised to 8-9 (van Ginkel *et al,* 1997b). With pulp and paper effluent attention was not only given to SRT and pH but also to the presence of the counterions iron and manganese. The laboratory results were confirmed in full-scale tests with wastewater from two different mills. In the first full-scale test, EDTA in the mill effluent originated from peroxide bleaching. Upon an increase of pH to 8.0 in the aeration basin an average EDTA reduction of 50% was achieved (van Ginkel *et al,* 1997b and 1999). The SRT of this treatment plant was only 10 days. The paper mill effluent was treated in a full-scale activated sludge plant operated at an SRT of approximately 25 days. Initially, the pH of the aeration basin of this plant was increased to 8.0, and, after 30 days, to 9.0. Results from the monitoring program demonstrated that the activated sludge plant adapted within seven days. After this week at pH 8.0, about 50% removal was found, which is attributed to biodegradation. A maximum EDTA reduction of about 80% was achieved at pH 9.0. An SRT of 10 days (plant treating wastewater from peroxide bleaching processes) and the Fe(III)EDTA complex may account for the partial removal (van Ginkel *et al,* 1997b, 1999). Finally, EDTA removal during activated sludge treatment under slightly alkaline conditions of a pulp and paper industrial effluent has successfully been attempted. The average removal was 76% and the minimum and maximum removals were 68% and 83%, respectively (Kaluza *et al*, 1998).

Conclusions
Although EDTA is not degraded in most standard biodegradability tests, it is clear that this compound can be removed in the environment by both growth-linked biodegradation and cometabolic transformation. Moreover, it is possible to demonstrate EDTA degradation in officially recognised standard tests by slightly increasing the pH or using water from, e.g., a river as inoculum. These recent standard test results confirm findings obtained with pure cultures capable of growing on EDTA. Based on these findings it should be concluded that EDTA is inherently biodegradable and that the biodegradation process results in complete mineralisation. Most monitoring studies to assess degradation of EDTA in plants treating domestic waste water demonstrate that EDTA is not removed. However, full-scale activated sludge systems treating industrial wastewater are operated to remove EDTA, as is indicated by the results obtained in a number of plants treating either pulp and paper or Industrial and Institutional (I&I) cleaning effluents. Alkaline conditions and an SRT>12 days are crucial to obtaining EDTA removal in sludge plants and it appears that counterions affect EDTA removal. These monitoring studies demonstrate that substantial amounts of EDTA used industrially is biodegraded and only part of the EDTA is discharged into the environment.

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Tabel 1: Overview of monitoring results from five full-scale activated sludge plants

Plant	Wastewater	pH	SRT (days)	Removal (%)	Comments
I	dairy	7.5-8.1	~20	90	
II	beer	7.3-7.7	~23	50	Treatment system too complex for interpretation
III	dairy	7.8-8.4	~9	30	SRT too low
IV	dairy	7.5-7.8	~40	35	Temperature (5°C) too low for EDTA-utilising bacteria to maintain themselves
IV	dairy	7.8-8.0	~40	95	
V	dairy and domestic	6.9-7.1	~20	0	Neutral pH does not support growth of EDTA-utilising bacteria
V	dairy	8.7-8.9	20	95	Laboratory CAS test at high pH

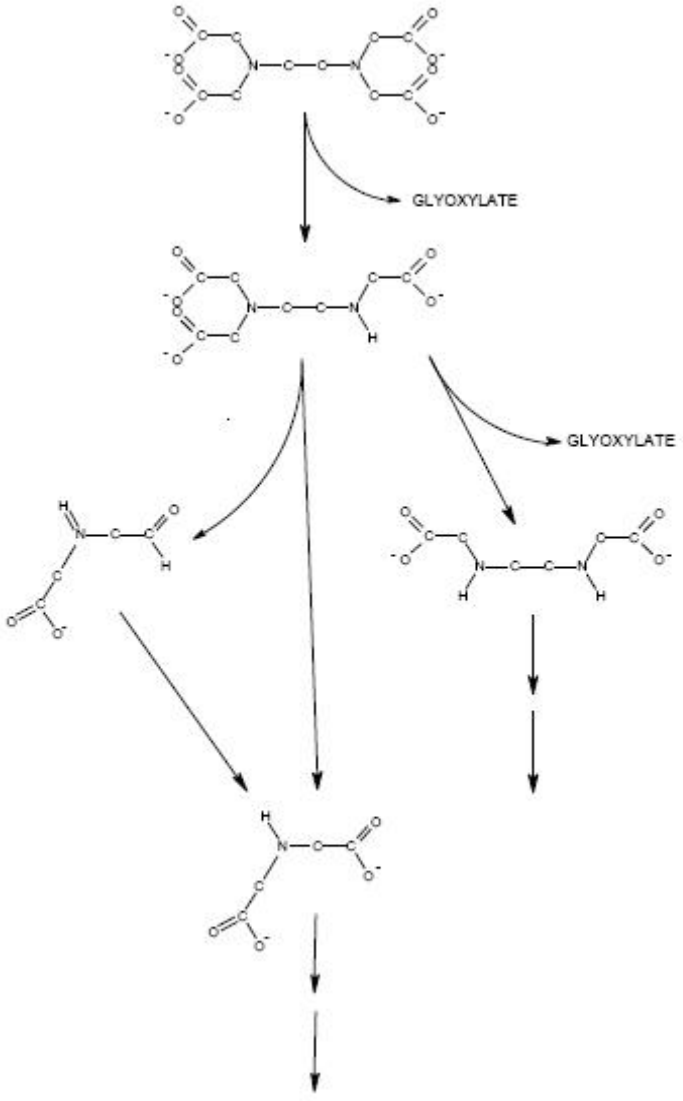

Figure 1: Proposed degradation pathways of EDTA.

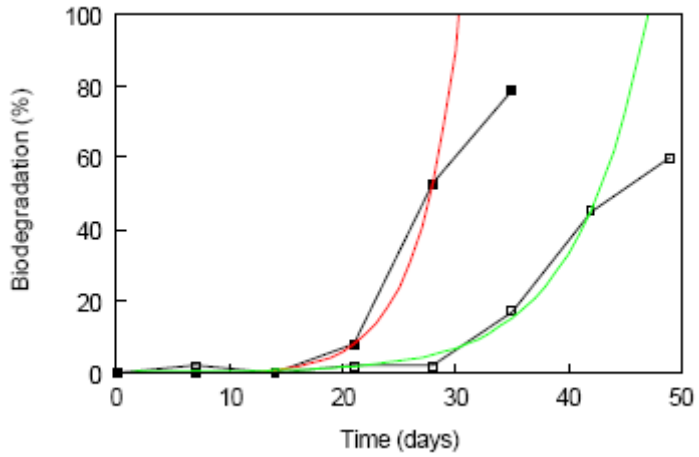

Figure 2 Percentage of biodegradation of $CaNa_2EDTA$ at pH 6.5 (□) and pH 8 (■) versus time in Closed Bottle tests inoculated with water from a lake. The half-lives were determined on the basis of the exponential curves, excluding the lag period, calculated from the measured data.

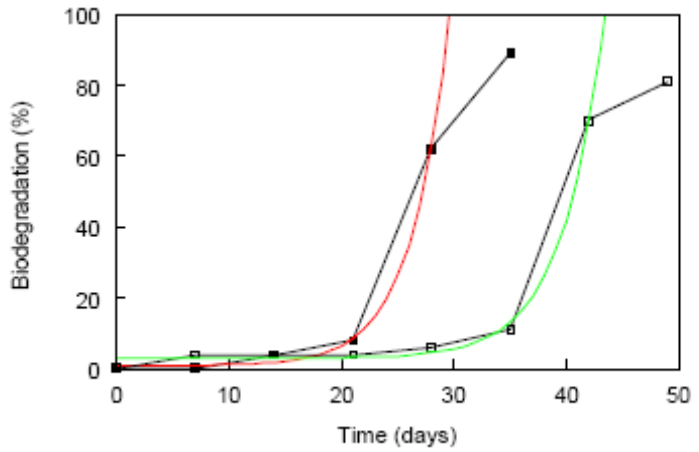

Figure 3 Percentage of biodegradation of $CaNa_2EDTA$ at pH 6.5 (□) and pH 8 (■) versus time in Closed Bottle tests inoculated with water from a ditch. The half-lives were determined on the basis of the exponential curves, excluding the lag period, calculated from the measured data.

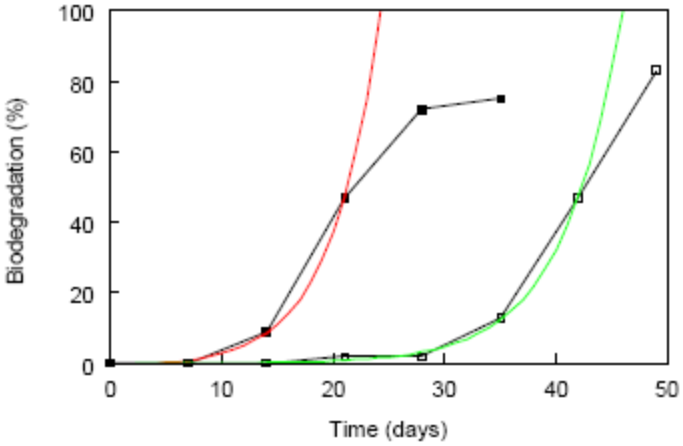

Figure 4 Percentage of biodegradation of $CaNa_2EDTA$ at pH 6.5 (□) and pH 8 (■) versus time in Closed Bottle tests inoculated with water from a river. The half-lives were determined on the basis of the exponential curves, excluding the lag period, calculated from the measured data.

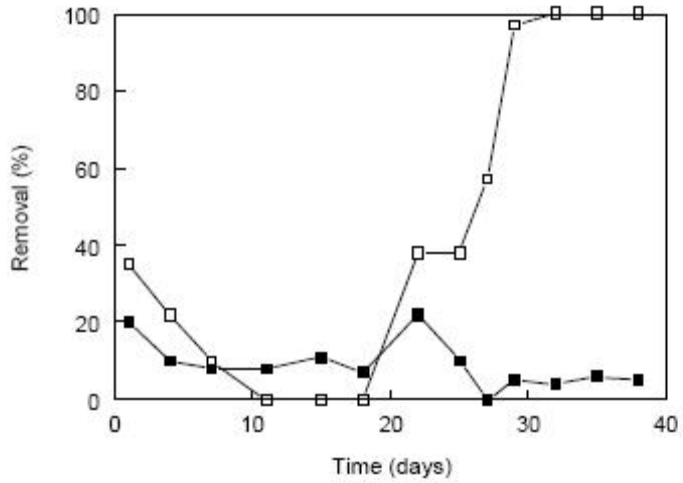

Figure 5 Removal by degradation of EDTA (65 mg/l.) added to domestic wastewater in SCAS units, run at pH 6.5 (■) and 8.5 (□).

AkzoNobel
Functional Chemicals

USA Risk Characterization Summary

As a member of the American Chemistry council (ACC) in the USA, AkzoNobel is committed to an international program, the Global Product Strategy (GPS), which is designed to improve product stewardship actions and to increase public awareness and confidence that chemicals in commerce are safely managed throughout their lifecycle. An important part of the AkzoNobel GPS program is completing risk characterizations for the chemicals it manufactures and imports, prioritizing chemical risks, recommending risk management actions where indicated, and making chemical health and safety information available to the public. [NOTE: The AkzoNobel GPS includes a number of product regulatory compliance programs (e.g., product safety for Material Safety Data Sheets and labels) that have been effectively functioning for many years.]

The AN Risk Characterization process in the USA is a team effort within the company. We:

(1) collect available health and safety information on the chemicals we manufacture and import,
(2) evaluate the chemical/physical, human health and environmental hazards presented by our chemicals,
(3) assess the human and environmental exposure to our chemicals, including customer use and disposal when this information is available,
(4) assess the potential risks ofpotential harm to human health and the environment, and,
(5) prioritize our chemicals according to the level of risk so that additional risk reduction actions can be recommended as needed.

One of the primary objectives of the AN Risk Characterization process is to identify those chemicals that present the highest risk and then to focus on ensuring that these chemicals are carefully managed to control these risks. AkzoNobel reviews the type and degree of hazard in view of the chemical use as well as customer practices to decide whether a chemical should be considered a high priority chemical. Generally, AkzoNobel uses the following factors in deciding whether a chemical should be considered a high priority: (1) *a high hazard potential* (acute or chronic), (2) *a high exposure potential* with respect to number of pounds manufactured or imported, or due to the type of customer application/use, or (3) *a combination of these two factors.*

When a chemical has been identified as a high priority chemical, AkzoNobel will make publicly available a product stewardship summary for the chemical that generally presents the hazards,exposures, risks and recommended risk management actions that should be taken. After the evaluation of high priority chemicals has been completed, AkzoNobel will address medium and low risk chemicals in the same type of process.

AN Risk Characterization process/07-2009/000

Overview of the useful applications of Ferrazone®

All food chemists know that the addition of iron to food can often cause problems with respect to iron taste, catalyzing breakdown of the food components, discoloration, and similar difficulties. Ferrazone® is much easier than most iron compounds to incorporate into food. It is fully and readily water soluble, it is tasteless, it generally causes little or no color change at normal addition levels (completely clear in water), is stable over most cooking temperatures, has a long shelf life, is generally not very reactive to food components, and generally does not react with other added vitamins and minerals. Ferrazone® has been successfully used at high doses (1600 ppm) in condiments like soy sauce and fish sauce (as recommended by WHO), and at lower doses in drinks (powdered and ready-to-consume), wheat and maize flour, biscuits, noodles, snacks, energy drinks, among many others.

1. What is Ferrazone® ?
Ferrazone® is Akzo Nobel's brand name for sodium iron (III) ethylenediaminetetraacetate (NaFeEDTA). It is also commonly known as sodium feredetate.

2. Why is Ferrazone® the preferred iron source to treat iron deficiency anemia?
Among the commonly used iron salts, Ferrazone® has several significant advantages. Ferrazone® is the preferred iron source to treat iron deficiency anemia because:
- it has a higher absorption rate in the human body
- it has no negative influence on the bioavailability of other minerals
- it can be added unobtrusively to several food vehicles
- it is stable under adverse storage and cooking conditions
- it is highly bioavailable and is least affected by absorption inhibitors, especially in phytate-rich diets
- it poses no risks of iron overload, and
- it exhibits minimal gastrointestinal disturbances.

3. What is the relative bioavailability (RBV) of Ferrazone® as compared to other iron sources?
Numerous iron absorption studies comparing the bioavailability of various iron sources and Ferrazone® (NaFeEDTA) have been conducted over the past several years. It is generally accepted that the RBV of Ferrazone® is 200~300. Ferrous sulfate, the commonly used iron salt, has an RBV of 100.

4. Has the efficacy of Ferrazone® been tested on a large scale?
Several comprehensive population trials in Thailand, Guatemala, Vietnam, China and South Africa highlight the therapeutic efficacy of Ferrazone®. A daily dose as low as 5 mg Fe (as Ferrazone®) per person has been demonstrated to be effective in improving the iron status (Hb) above the cut off level within three months.

5. Is the latest safety data available on Ferrazone®?
A comprehensive study on the disposition, accumulation and toxicity of iron in rats was conducted by Appel et al. in 2000. They administered $FeSO_4$ and FeNaEDTA in rats via the diet for 31 and 61 days. Clinical signs, body weights, food consumption, food conversion efficiency, hematology, clinical chemistry and pathology of selected organs were used as criteria for disclosing possible harmful effects. Iron is accumulated from the diet in liver, spleen and kidneys in a dose-dependent manner. Iron derived from FeNaEDTA was taken up and/or accumulated less efficiently in liver and spleen than iron from $FeSO_4$. Moreover, feeding iron up to 11.5 and 11.2 mg/kg body weight/day, derived from $FeSO_4$ and FeNaEDTA, respectively, did not result in tissue iron excess or in any other toxicologically significant effects.

6. How is Ferrazone® metabolized in the human body?
When Ferrazone® is ingested, it passes the stomach intact. Subsequently it arrives in the duodenum and small intestine, where the absorption into the blood circulation of iron and other minerals takes place. The mucosa cells that line the duodenum and small intestine possess the remarkable capability to split Ferrazone® into iron and EDTA molecule. The iron molecule is absorbed into the body, while EDTA molecule stays behind and is finally excreted via the stool. A small part (5%) of this split-off EDTA is able to enter the blood circulation, but is quantitatively excreted by the kidneys within 24 hours. Less than 1% of the sodium feredetate enters the blood circulation, but the kidneys quickly and completely remove it as well.

7. Since the body absorbs the iron in Fe^{2+} (ferrous) form, why a Fe^{3+} (ferric) form from Ferrazone® absorbable in the human body?

Under ambient conditions, most ferrous salts are soluble in water, whereas their ferric counterparts are not. Since iron bioavailability to a major extent is a function of solubility, ferrous salts rank among the most effective iron supplements known to-date. Likewise, it is known that the mucosa cells take up iron from the lumen as ferrous ions and not as ferric ions. Nevertheless, these very same cells can readily convert ferric ions into ferrous ions. Therefore, an effective iron source does not necessarily need to be in the ferrous form. It can be in the ferric form as well provided the ferric salt is sufficiently soluble in water.

8. What is the effect of Ferrazone® on taste, side-effect and effectiveness?

Iron compounds are usually associated with undesirable metallic taste and have been known to cause gastro-intestinal problems. To avoid the occurrence of metallic taste would require lowering the content of iron compound in the supplement. Unfortunately, this would render the supplement ineffective. Due to its remarkable bioavailability, Ferrazone® effectively eliminates the dilemma of effectiveness vs. bad taste and gastrointestinal side effects.

9. What is the regulatory status of Ferrazone®?

Ferrazone® is specified in British Pharmacopoeia 2001. It is sanctioned by JECFA in 1999.

10. LITERATURE

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N.B.: More details regarding the use of Ferrazone® in beverages, in powdered beverage, in ready-to-eat breakfast cereals, in coffee, in curry powder, in drinking water, in fish sauce, in soy sauce, in sugar, in wheat flour and in pharmaceutical supplements and a lot of literature references can be found on www.ferrazone.com.