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FROM DATA TO DECISION

A case study of controversies in cancer risk assessment

Doctoral Thesis

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ABSTRACT

Risk assessments serve as the foundation of policy decisions on whether to take measures to reduce a risk or not. However, different risk assessors frequently come to divergent estimates of the magnitude and even the nature of risks. Few attempts has been made in the past to describe and understand the reasons for these differences.

This thesis reports the results from a detailed comparison of 30 different cancer risk assessments made of one and the same chemical substance, namely the chlorinated solvent trichloroethylene (CAS no. 79-01-6). The purpose of the present study is to discuss (1) why risk assessors come to different conclusions, (2) how scientific data are used in risk assessment, and (3) how scientific uncertainty is handled in the process. The overall objective is to contribute to increase the transparency and reliability of risk assessments so that they better serve the needs of risk managers and the public.

In the first part of this study the different conclusions drawn in these risk assessment documents are identified and described. This is made within the framework of a proposed cancer risk assessment index (CRAI). The CRAI categorization shows that these risk assessors come to divergent conclusions about the trichloroethylene potential to cause cancer. To enable an analysis of the reasons for these differences, detailed information from the trichloroethylene risk assessment documents was stored in a database. This information made it possible to compare the risk assessment documents in terms of data availability (a time dependent factor), data selection, data interpretation, data quality evaluation, and (animal to human) extrapolation of data, and to analyse how these parameters influenced the overall conclusions.

The analysis of these data indicates that the differences in conclusions cannot exclusively be explained by an evolving database (data availability). The data sets utilized by the trichloroethylene risk assessors are surprisingly diverse and incomplete, and biased data selection may have influenced some of the risk assessors' conclusions. The TCE risk assessors often interpret and evaluate scientific data in different ways. These differences are considered to be within the scope of the scientifically acceptable.

In the second part of this case study the European Union regulatory process for classification and labeling served as study object of the risk assessment process in a setting where risk assessors from different affiliations evaluated exactly the same data. This part of the study indicates that there is a scope of possible interpretations of the primary data in relation to the classification criteria and thus that there may be more than one possible alternative for classification of individual substances. The main controversies in this process are also identifed and they are found to concern issues that include policy considerations and thus are not readily resolved by further research.

It is concluded that the uncertainty inherent in scientific data opens up a scope of possible interpretations and conclusions and that differences in the assessment and handling of this scientific uncertainty have the potential to influence the overall assessment of risk.

It is furthermore concluded that even if an enormous amount of resources were spent on testing and assessment of individual substances (orders of magnitude more than what is required according to existing and proposed regulations), significant uncertainty about their potential to cause harm may still remain.

LIST OF PUBLICATIONS

I. Rudén C. (2001) "The use and evaluation of primary data in 29 trichloroethylene carcinogen risk assessments", *Regulatory Toxicology and Pharmacology* 34(1):3-16.

II. Rudén C. (2001) "Interpretations of primary carcinogenicity data in 29 trichloroethylene risk assessments", *Toxicology* 169(3):209-225.

III. Rudén C. (2002) "The use of mechanistic data and the handling of scientific uncertainty in carcinogen risk assessment – the trichloroethylene example", *Regulatory Toxicology and Pharmacology* 35(1):80-94.

IV. Rudén C. "Scrutinizing three trichloroethylene carcinogenicity classifications in the European Union – Implications for the risk assessment process", accepted for publication in *International Journal of Toxicology*.

V. Rudén C. "Science and transscience in carcinogen risk assessment – the European regulatory process for trichloroethylene", accepted for publication in *Journal of Toxicology and Environmental Health, Part B: Critical Reviews*.

CONTENTS

LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
CRAI	Carcinogen risk assessment index
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of Notified Chemical Substances
EU	European Union
GLP	Good Laboratory Practices
In vitro	Literally: "In glass", i.e. studying biological processes in laboratory aparatus.
In vivo	Describing biological processes as they are observed in their natural environment, i.e. within whole living organisms.
LD_{50}	The single oral dose that is lethal to 50% of a group of experimental animals
LC_{50}	The single inhaled dose that is lethal to 50% of a group of experimental animals
LOAEL	Lowest observed adverse effect level
NOAEL	No observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent, Bioaccumulating and Toxic
POPs	Persistent Organic Pollutants
REACH	Registration, Evaluation and Authorisation of Chemicals, i.e. the new strategy for a future chemicals policy proposed by the European Commission (2001).
SIDS	Screening Information Data Set
TCE	Trichloroethylene
VPVB	Very Persistent and Very Bioaccumulating

The abbreviations used in this thesis to denote the risk assessment documents under study are explicated separately in the list of references.

Keywords:
Regulatory toxicology, risk assessment, risk management, chemicals control, mechanism of carcinogenicity, trichloroethylene, CAS No. 79-01-6, chlorinated solvents

1 INTRODUCTION

This is a thesis in regulatory toxicology. Regulatory aspects of toxicology encompass the chain of activities from the generation of primary toxicity data, via the interpretation and evaluation of data in risk assessment, to risk management. The purpose of regulatory toxicology is to help bridge the gap between scientists and regulators, and its overall objective is to protect health and the environment against harmful effects of chemical substances (Schwenk *et al* 2002).

Risk assessments serve as the foundation of regulatory decisionmaking on whether to take actions to reduce (or otherwise manage) a risk or not. Risk assessments of chemicals are made on national, regional and international bases and different risk assessors frequently come to divergent estimates of the magnitude and even the nature of risks. Few attempts have been made in the past to describe and understand the reasons for these differences. In-depth studies of the crucial issues of interpretative practices and scientific uncertainty in chemical risk assessment require toxicological training and should be made within the community of toxicologists. A deeper understanding of the risk assessment process may help increase the transparency and reliability of risk assessments so that they better serve the needs of risk managers and the public. As far as we know, the case study that constitutes this thesis is unique in its kind.

In section 2 the underlying problem with widespread chemical pollution is briefly described. Section 3 outlines the European Union regulatory process for general (industrial) chemicals. This section contains a brief introduction to toxicity testing and the uncertainty inherent in toxicity test methods (3.1), an outline of the process of risk assessment of chemicals (3.2), and an introduction to the risk management process summarizing central parts of the European Union chemicals legislation (3.3). Section 3.4 introduces the precautionary principle. In section 4 the aims, methods and results of the trichloroethylene case study are reported on (4.1-4.4), and some concluding remarks are presented (4.5).

2 BACKGROUND

2.1 COMPLEX EXPOSURE...

The global production of chemical substances amounts to over 400 000 000 metric tonnes per year and the European Union (EU) is the world's largest chemical producer covering more than 30% of the total market (European Commission 2001). More than 2 500 chemicals are produced in or imported into EU in very high volumes, i.e. quantities exceeding 1 000 tonnes per year (ecb.jrc.it), and some 30 000 substances are marketed in volumes exceeding 1 tonne per year (per manufacturer) (European Commission 2001).

The number of different chemical substances available on the EU market has been estimated to lie between 30 000 and 100 000. The number of chemical products (mixtures of chemicals) is unknown, but certainly orders of magnitude higher. Hence, chemical substances are abundant. Almost every sector of modern society depends in some way on chemicals and the potential for human exposure is correspondingly widespread. More precise knowledge about the nature and magnitude of human chemical exposure is to a great extent lacking (Allanou *et al* 1999). The complexity of exposure is increased by the fact that many anthropogenic substances are metabolized in both man and other organisms, sometimes giving rise to metabolites that are more toxic than the original compound.

2.2 ...WITH UNKNOWN EFFECTS

A major problem with widespread chemical pollution is that the effects of most chemical substances on the environment and human health are unknown. This is true irrespective of their use e.g. in production or in products, or of their distribution in waste or in wasted material.

In 1984, the U.S. National Academy of Science reported that 78% of the chemicals that were commercially used in high volumes (i.e. more than 1000 tonnes per year) did not even have base-set toxicity data (NRC 1984). An update of this study performed by the Environmental Defense Fund thirteen years later, indicated that there had been no significant improvement; 71% of a random sample of 100 U.S. top-volume commercial chemicals lacked basic data from toxicity testing (Roe *et al* 1997). Furthermore, a recent report from the European Commission showed that 79% of the 2 500 EU high production volume chemicals have less than base-set data (Allanou *et al* 1999).[1]

Extensive toxicological knowledge is only available for a handful of chemical substances and knowledge about adverse health effects from exposure to mixtures of chemicals is almost completely lacking.

An ambitious initiative to increase data generation has been taken in the USA through an agreement between the U.S. Environmental Protection Agency, the Chemical Manufacturer's Association, and the Environmental Defense Fund, i.e. the Chemical Right-to-Know Initiative (ChemRTK), announced in 1998. By this agreement some 500 companies have voluntarily committed to provide basic

[1] A description of what is included in a "base-set" of toxicity tests is provided in the forthcoming section on risk management of New chemicals.

toxicological testing for more than 2000 of the U.S. high production volume chemicals (www.epa.gov/chemrtk/).

In Europe there are currently no general test requirements for the industrial chemicals representing about 99% of the production volume, but the responsibility for the European chemical industry to generate toxicity data for previously untested existing chemicals will increase according to the new proposed strategy for a future European chemicals policy (European Commission 2001). However, the test requirements for the majority of substances will be limited. Therefore, despite these initiatives, significant data gaps will remain.

3 THE REGULATORY PROCESS

3.1 TOXICITY DATA AND SCIENTIFIC UNCERTAINTY

Health risk assessments of chemicals have to be based on scientific data. Toxicity data can be obtained either from experimental systems such as *in vitro* assays or *in vivo* animal experiments, or from epidemiological studies of exposed humans.

The use of toxicity data for risk assessment purposes involves scientific uncertainty. Such uncertainty can be related to the study methods e.g. to (1) the quality of the planning, performing, and reporting of individual studies, (2) lack of knowledge about the relevance of the individual study results, i.e. uncertainty about whether the effects seen in the study is causally connected to the exposure of interest or not, or (3) statistical uncertainty. Additional scientific uncertainty is added in the risk assessment process. I.e. (4) uncertainty pertaining to extrapolations, i.e. lack of knowledge about the relevance of the individual study results to human risk assessment, and (5) to lack of important data.

Statistical uncertainty is further discussed in section 3.1.3., and uncertainty pertaining to extrapolations are discussed in sections 3.2.1 (dose extrapolation) and 3.2.2 (species extrapolation).

3.1.1 Toxicity data obtained from experimental methods

In toxicological research the experimental methods are designed to serve specific research purposes. The toxicologist in academia may thus choose the best scientific method available on a case-by-case basis. In contrast, for routine toxicity testing the use of standardized test methods is preferred since it facilitates comparisons of results for different substances e.g. when applying criteria for classification and labeling of chemicals.

The procedures for designing, performing and reporting standardized toxicity tests are laid down in official guidelines, such as the OECD guidelines. There are many different types of standardized animal bioassays. They differ e.g. in the number of animals used, in the duration of exposure and in which endpoints are studied. Below three types of standard assays are briefly outlined: acute toxicity, sub-acute toxicity and chronic toxicity/carcinogenicity.

Previously, the standard study for acute toxicity testing was the LC_{50} or LD_{50} test. This test was designed to estimate the magnitude of the single dose of a chemical that is lethal to 50% of exposed experimental animals. This method involves the administration of very high doses and it has been criticized because of animal welfare considerations. The currently preferred methods for acute toxicity testing require fewer animals, and since "evident toxicity" is a valid endpoint (besides mortality), the doses in these tests can be kept lower and animal suffering can thereby be reduced.

Acute tests require a limited amount of resources and therefore such data are available for many substances. The data obtained from these tests provide information about the immediate toxicity of substances and are important for the classification and labeling of chemical substances. However, data on the toxicity caused by a single high dose provide little knowledge about adverse effects due to long-term and low-dose exposure. Information about this is also needed for human health risk assessment.

According to the OECD guidelines for sub-acute toxicity testing three groups of animals, each consisting of at least 5 males and 5 females, are required for this type of

test. Two groups receive a low and a higher dose respectively, administered daily for 28 days, and the third group serves as an unexposed control group. In this type of study, the total number of animals is thus about 30. The cost of performing a 28-day study is about 50 000 – 80 000 Euro. Sub-acute toxicity data are available for only a small portion (perhaps 15-20%) of the European Union high volume chemicals (Allanou *et al* 1999).

In a full chronic toxicity and carcinogenicity study at least 50 animals per sex and group in three groups, i.e. a total of at least 300 animals is required. The animals are dosed during the majority of their life span, which for rodents means between 1,5 and 2 years. This type of study is thus both time and resource consuming. The cost of performing a full scale chronic and carcinogenicity test lies between 600 000 and 1 500 000 Euro (depending e.g. on the chosen species and exposure route). Therefore chronic toxicity/carcinogenicity data are only available for few substances.

3.1.2 Epidemiology – data from human exposure

In epidemiology the effects on humans exposed to chemical substances (and other agents) are studied. Epidemiology is an observational and not an experimental science. Epidemiologists study exposures and disease occurrence in a real-life setting, and are thus depending on a multitude of influences (a myriad of exposures, genetic aspects, human behaviour, and life-style factors etc), many of which are interrelated and have strong confounding potential. The design of an epidemiological study has therefore to be determined depending on the prerequisites available.

Two main types of design are case-control studies and cohort studies. Cohort studies are exposure based, i.e. the occurrences of disease or mortality among exposed and non-exposed individuals are compared. Case-control studies on the other hand are outcome based, i.e. the exposure of humans that have contracted a disease is compared to the exposure of a group of healthy subjects. Both types of studies provide an estimate of relative risk (ratio of incidence or mortality in those exposed to incidence or mortality in those not exposed) as the main measure of association.

The advantages of using epidemiological data in risk assessment is that no species extrapolation of the data is necessary since the exposed individuals and the size and nature of exposure are directly relevant to the assessment of human risk.[2] Therefore, epidemiology provides important contributions to a health risk assessment and (high quality) epidemiological data are usually assigned significant weight in the risk assessment process. The main disadvantage is of course that these data become available only after humans have been exposed and potentially injured due to this exposure.

Due to the obstacles in designing these studies, we can expect conclusive epidemiological data to become available only for a limited number of substances. Therefore, health risk assessment (and risk management) of chemicals cannot depend on the availability of epidemiological data.

Applying our increasing understanding of the mechanisms underlying toxicity and carcinogenesis and combining the methodologies of molecular biology, genetics and epidemiology has the potential to increase the validity and precision of

[2] This does however not mean that the exposure situation for workers is similar to the exposure of the general population, and neither does it mean that the exposed workers are representative of the population at large (which includes e.g. children, older people, and people with different kinds of disease).

epidemiology and further strengthen the impact that these data have in risk assessment (Trichopoulos and Adami 1998).

3.1.3 Statistical uncertainty

A general problem with toxicity data is that even though it is often possible to show convincingly that a substance has a particular adverse effect (e.g. by generating a convincing set of epidemiological data), it can rarely be proven beyond reasonable doubt that a substance does not have a particular adverse effect. The main reason for this is that for serious health effects we care about risks that are small in terms of study statistics. As a rough rule of thumb, epidemiological studies cannot reliably detect excess relative risks about 10% or smaller, and in many cases excess rates much higher than 10% may go undetected. For the more common types of cancer in industrial countries, lifetime risks are between 1% (leukemia) and 10% (breast cancer in Swedish women). Therefore, even in the more sensitive studies, the limits of an observable excess lifetime risk are in the order of 1/100 or 1/1000. These are risks that in many cases are considered unacceptable (Vainio and Tomatis 1985, Hansson 1997). The problem with low sensitivity is most pronounced for diseases with a high background incidence or, in epidemoiology, when the effects are caused by common exposures. Consider for instance the following theoretical epidemiological example: Exposure to substance A causes an increased incidence of leukemia, from 1,0% (the background incidence) to 1,5%. The effect of exposure to substance A can very well be detected in a well-designed epidemiological study. Exposure to substance B results in an increased incidence of breast cancer from 10% (the background incidence) to 10,5%. Hence, the number of additional cases is the same as in A, but due to the relatively high background incidence, an increase in 0,5% is not statistically distinguishable from normal variation. Hence the effect of substance B is not detectable even in a well-designed epidemiological study (Hansson 1999).

A similar limitation exists for experimental (animal) data. The size of the exposed groups in animal experiments are usually $\leq$100, therefore excess risk smaller than 1/100 is not detectable in these experiments even in the cases when the background incidence is close to zero. If the background incidence is higher detectability decreases. It has for instance been estimated that a study designed to detect an increased mutation frequency of about 0,5% after low dose radiation would require an experiment using 8 000 000 000 mice (Weinberg 1972).

It is thus clear that even biologically significant risks may go undetected in toxicity tests, and furthermore, it should not be expected that all human carcinogens have sufficiently large effects to be detectable in epidemiological studies.

3.2 RISK ASSESSMENT

Health risk assessments may have different aims and scopes, but they always include an attempt to identify the potential adverse effects that a substance may cause in humans. This encompasses a description of the nature of these effects and some estimation of the likelihood that they will occur as well as of their extent or severity (European Commission 1996 and NRC 1994).

According to the general theoretical model, the process of risk assessment is usually divided into four steps. (The exact terminology used for the different parts of the process varies between countries and organizations, but the contents of the different steps are basically the same in the U.S. and the EU models (NRC 1983 and European Commission 1996).)

The first step consists of ***hazard identification***, and this part of the process aims at determining the inherent properties of a substance, i.e. a substance's potential to cause harm in an experimental animal or in the human body (e.g. the potential to cause cancer). This part of the risk assessment does not take exposure into account and therefore it does not estimate the magnitude of the risk.[3]

The next step is the ***dose-response assessment.*** The purpose of the dose-response assessment is to describe the relationship between the administered dose and the response of the experimental animals. This assessment can be in the form of a *dose-response* relationship, which is the relationship between the administered dose and the percentage of experimental animals that exhibits a toxic effect of concern. It could also be reported as a *dose-effect* relationship, which is the relation between the administered dose and the severity of an effect of concern (e.g. the average liver weight in a group of experimental animals). The term dose-response relationship is used here in a broad sense, covering both dose-response and dose-effects relationships.

The concept of dose is central in toxicology (virtually any substance can be toxic at high enough dose) and characterizing the dose-response relationship is a major part of risk assessment procedures. Two main types of theoretical dose-response relationships are commonly referred to: with or without a threshold dose for adverse effects. For choosing a risk management strategy it is often crucial whether the dose-response curve is considered to be linear from zero exposure or if a threshold dose is anticipated, and in that case, what is the level of the threshold. Usually for mutagenicity, genotoxicity and genotoxic carcinogenicity a linear (non-threshold) dose-response relationship is assumed, while for carcinogens shown to exert an epigenetic mechanism of action, a threshold approach may be applicable. Characterizing the dose-response relationship may involve the application of mathematical models.

Ideally the critical effect should be identified, i.e. the adverse effect that occurs at the lowest dose. The idea behind characterizing the dose-response relationship for the critical effect is that if regulations are sufficient to protect against the critical effect, then the risk of other effects should be negligible. The critical effect may however differ between species, and the correctness of identification also depends on the sensitivity of the test system to detect the critical effect, for example due to variability within the experimental species, the number of animals per dose group and the choice of dosing regimen in the test. In practice the definition of a critical effect is often the adverse effect seen at the *lowest experimental dose*, but other definitions have also been proposed, one example being *the effect determining the ADI* (acceptable daily intake). That is, the effect that gives rise to the lowest ADI when dividing the NOAEL (no observed adverse effect level) for this effect with an appropriate uncertainty factor.

The third step of the risk assessment process is the ***exposure assessment***. The exposure asessment initially aims at determining the likelihood of human exposure (1) in the workplace, (2) through consumer products, and (3) indirectly via the environment (European Commission 1996). Next, the objective is to estimate the magnitude and duration of the doses that humans may receive, as well as the potential exposure routes. This part of the exposure assessment have to be based on measured data and/or the use of theoretical exposure models.

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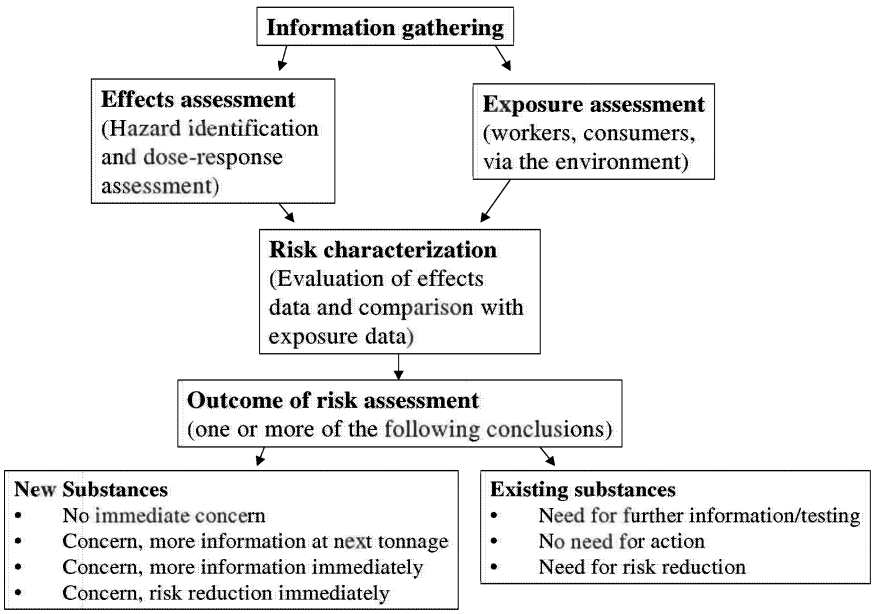
[3] The term "risk" is commonly defined as the probability that an unwanted event will occur multiplied with the value of its negative outcome. In toxicological risk assessment this term usually has a broader and looser definition, not involving the use of probabilities.

The final step is ***risk characterization***, which involves comparing the quantitative or qualitative information on human exposure to the NOAEL or LOAEL for the critical effect (ususally derived from animal studies), or when appropriate, a qualitative evaluation of the likelihood that an effect will occur at any given exposure.

If human exposure is estimated to be higher than the NOAEL/LOAEL, the substance is considered "of concern" (European Commission 1996). If exposure is estimated to be less than the animal derived NOAEL value, then the "margin of safety" must be assessed (i.e. the magnitude by which the NOAEL or LOAEL exceeds the estimated exposure). How large margin of safety that should be required is assessed by "expert judgement" on a case-by-case basis, taking into account e.g. scientific uncertainty, the nature and severity of the effect, the nature of human exposure etc. (European Commission 1996).

FIGURE 1. *Outline of the risk assessment process according to the Technical Guidance Document on risk assessment of new and existing chemicals (European Commission 1996).*[4]



3.2.1 Dose extrapolation

In experimental systems the study design can be adjusted to increase the possibility to detect rare effects by increasing the dose levels. Therefore, toxicity data generated by standard bioassays are usually obtained from exposures that are significantly higher than what is directly relevant to human risk assessment. At high (experimental) doses

[4] This Technical Guidance Document is currently being revised.

metabolic pathways may become saturated and thereby cause alterations in the relative rates of metabolism through different enzyme systems compared to the low dose situation, sometimes leading to a relatively higher proportion of the administered substance being metabolically activated to more toxic molecules. To compensate for this an extrapolation of data from the experimental high dose to the relevant dose range is made. This extrapolation increases the uncertainty of the assessment unless it can be convincingly shown that the effects and mechanisms of toxicity are the same in the high dose region as for low doses. In the absence of metabolic and mechanistic information at various dose levels it is cautious (i.e. health protective) to assume that the effects and mechanisms seen at the high (experimental) dose levels are relevant to low dose exposure.

3.2.2 Species extrapolation

A crucial task in risk assessment is to extrapolate data from bioassay experiments to assess the human risk. It is generally presumed that toxic and carcinogenic effects seen in mammalian test species are relevant to humans since the physiology of the common test species are similar to humans. However, both qualitative differences (i.e. in the degree of the response) and quantitative species differences (i.e. in the nature of the response) have been shown to exist.

Many substances must first be metabolized to reactive electrophilic compounds to exert their toxic (including carcinogenic) potential, and quantitative species differences often have a metabolic basis (Dybing and Huitfeldt 1992). The accuracy of quantitative species extrapolation can therefore be increased by using simple conversion factors correcting for differences in metabolic rate, or by using physiologically based kinetic modeling to assess the concentration of the administered compound (or of the relevant metabolite) in the target tissue.

Two mechanisms generally considered to give rise to qualitative species differences in carcinogenic response is receptor-mediated rodent specific liver carcinogenicity caused by peroxisome proliferating agents (Reddy and Rao 1992), and male rat specific α-2μ-Globulin nephropathy (Swenberg *et al* 1992).

Obviously, both under- and overestimation of human risk can result from interspecies differences. One way of handling the uncertainty that lack of knowledge about potential species differences gives rise to is to apply default assumptions. Default assumptions are scientifically based, but policy influenced "rules of thumb" on how to overcome lack of data or scientific uncertainty when extrapolating from experimental data to human hazard estimation (U.S. EPA 1999). The application of default assumptions has been much discussed in carcinogen risk assessment.

Examples of qualitative default assumptions are:

- In the absence of adequate data on humans, it is biologically plausible and prudent to regard substances for which there is sufficient evidence of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans (IARC 1999).

And:

- If adequate studies in two species are available which show that a substance is not carcinogenic, then this suggests lack of carcinogenic potential. This

conclusion is "inevitably limited to the species, tumor sites and levels of exposure studied" (IARC 1999).

Some defaults are risk aversive while others may underestimate the response (e.g. in the most sensitive part) of the human population. Some of them are implicit, but preferably they should be explicitly defined as well as the (scientific and non-scientific) justifications for using (and departing from) them.

Since the purpose of using a default assumption is to overcome data gaps and scientific uncertainty, new data and increasing knowledge have the potential to motivate a revision of the presumptions. One example of this is improved knowledge about carcinogenic mechanisms. As the understanding of critical biological events in the carcinogenesis process increases, the possibility to elucidate carcinogenic mechanisms, e.g. by studies of putative intermediate effects, or of cancer-correlated end-effects, also increases. This is reflected for example in the EU regulation for the classification and labeling of chemical substances in which it is stated that if the mechanism of experimental (animal) carcinogenesis is "clearly identified", with "good evidence" that this process cannot be extrapolated to man, then the substance should not be classified as carcinogenic (Council directive 67/548 EEC). According to the IARC the following criteria have to be fulfilled before concluding a carcinogenic mechanism irrelevant to humans: It should first be established for the particular tumor site that the mechanism in question is the primary one in the experimental species. Secondly it should be established that the same or a similar mechanism does not operate in humans, and third, if the agent induces other types of tumors in experimental animals, then the first two criteria would have to be fulfilled for each of those tumor sites (IARC 1992).

None of these criteria do however specify the amount or nature of evidence required for motivating such a revision of the initial assumption.

3.3 RISK MANAGEMENT

The starting-point of the risk management process is the outcome of risk assessment, which it combines with legal, economical, and technological information pertaining to various ways of reducing or eliminating the risk in question, and also with a political and social consequence analysis. Based on this, a decision is made on what measures – if any – should be taken to manage the risk.

Chemicals control in Europe is harmonized at the level of the EU. Therefore I focus this brief overview on central parts of the European Union legislation for general (industrial) chemicals. (Separate regulations apply to drugs, pesticides, biocides and food additives.)

3.3.1 Classification and labeling

The first steps towards regulation of chemicals in the EU was taken by the European Communities in 1967, when Council directive 67/548 on the classification, packaging and labeling of dangerous substances was adopted (Lönngren 1992). The classification and labeling system is a central part of chemicals control since it applies to all general chemicals and since the classification process constitutes the background for further risk assessments and risk management considerations of any given chemical. In fact, classification has in some cases direct implications for risk management since classification in some of the danger classes is directly coupled to risk management measures through down-stream regulations. One example of this is classification of substances as carcinogenic, mutagenic or toxic to reproduction in either of the two

highest classes (category 1 or 2). Chemicals classified in any of these categories may not be placed on the market for sale to the general public according to Council directive 76/769 (certain concentration limits for preparations apply).

The classification and labeling directive states that all chemical substances should be classified according to their chemical and toxicological properties. However, the rules include no testing requirements, i.e. the classifications are made on the basis of available data. This has the disadvantage that those substances that lack toxicity data will remain unclassified and unlabeled. (For further discussion about this problem, see Hansson and Rudén, in press).

The directive specifies criteria for the classification of substances into the following classes:

Physico-chemical properties:

- Explosive
- Extremely flammable
- Highly flammable
- Oxidizing

Toxicological properties:

- Very toxic
- Toxic
- Corrosive
- Harmful
- Irritant

Ecotoxicological properties:

- Dangerous for the environment

Substances that belong to any of these classes have to be provided with a warning label. The label contains a conspicuous danger symbol and, so called, risk phrases such as: "Very toxic in contact with skin", or "Danger of very serious irreversible effects".[5] In addition, safety phrases indicating how to safely handle the substance may be required. Examples of such phrases are: "Wear suitable protective clothing", and "Do not breathe dust".

The classification criteria list of a number of toxicological (and chemical) properties, and the danger class (with accompanying symbol) and risk and safety phrases that are assigned to substances with these properties (Commission directive 93/21/EEC). For a summary of the classification criteria see *Table 1*.

[5] The risk-phrases do not refer to risks in the conventional sense; they answer better to the description "hazard phrases".

TABLE 1. *Summary of the classification criteria for toxicological properties.*

Acute toxicity	**Carcinogenic Mutagenic Reproductive toxicity**	**Corrosion**	**Sensitiz-ation**	**Irritation**	**Danger class**	**Label symbol**
Very high acute toxicity					**T+ (Very toxic)**	
High acute toxicity	Cat.1-2				**T (Toxic)**	
		Skin destruction			**C (Corrosive)**	
Acute toxicity	Cat. 3		By inhalation		**Xn (Harmful)**	
			By skin contact	Skin, ocular, or respiratory effects	**Xi (Irritant)**	

The criteria for acute toxicity, irritation effects, and sensitization are relatively uncomplicated to apply, since they are based on quantitative data obtained from standardized test methods, such as the LD_{50}. In contrast, the criteria for carcinogenicity, mutagenicity and reproductive toxicity are less easily interpreted since they to a greater extent are criteria on the interpretation of qualitative data. This opens up a scope of scientifically acceptable interpretations of such data in relation to the criteria. The classification criteria for carcinogens are described in more detail in Paper IV.

3.3.2 New and existing chemicals

Before 1992 there were few restrictions or regulatory demands coupled to the marketing of general chemicals in the EU (except for classification and labeling), i.e. it was allowed to sell chemical substances without any prior testing, and no approval from the authorities was needed. During the 1960s and 1970s it was realized that this lack of chemicals control was not sustainable (Lönngren 1992) and the idea of introducing a mandatory notification procedure for new chemical substances (i.e. substances not previously marketed in the EU) was put forward in 1979 under the 6th amendment of directive 67/548 (Council directive 79/831/EEC).

In order to separate new substances from those already available on the market, the European Commission performed an inventory of all chemicals that were marketed or considered for marketing on the European market as of the 18th of September 1981. The result of this inventory is registered in the EINECS database (the European Inventory of Existing Commercial Chemical Substances). This is a closed database (no new substances are added), and substances listed in EINECS are in the regulatory context called "existing chemicals". General chemicals marketed after 1981 that are not listed in EINECS, are called "new chemicals". New and existing chemicals are regulated according to different legislations.

The regulation of new substances. There are currently about 2 700 chemicals regulated as "new" substances, representing about 1% of the total production volume (European Commission 2001).

The rules for notification and risk assessment of new substances were introduced in the 7th amendment of directive 67/548 (i.e. Council directive 92/32/EEC). According to these rules new substances shall be submitted to a test battery and a notification procedure before they may be put on the EU market. There are different test packages to be carried out depending on the amounts to be marketed annually. The base-set requirement for substances marketed in quantities exceeding 1 tonne per year (per manufacturer) includes data on physico-chemical properties, mutagenicity (*in vitro* testing), acute toxicity testing, skin and eye irritation, skin sensitization, and a sub-acute/28-day toxicity study. (For ecotoxicological properties acute toxicity tests on fish, *Daphnia* and algae and degradation data are required.) (Annex VII A of directive 92/32).

For substances marketed in lesser volumes a reduced data set, i.e. *in vitro* and acute toxicity testing, is required (Annex VII B and VII C of directive 92/32). When the quantity reaches 10 tonnes, 100 tonnes and 1000 tonnes per year per manufacturer additional testing is required (Annex VIII level 1-2 of directive 92/32).

The notification dossier is to be submitted to the national competent authority in the Member State where the notifier is located, and it shall include for example the results from the required tests, a proposal for the classification and labeling of the substance, and a proposal for a safety data sheet for classified substances.

The national competent authority checks that the notification conforms to the requirements of the directive and carries out a risk assessment of the substance (according to the general principles laid down in Commission directive 93/67/EEC). A summary of the notification dossier, a proposal for the formal classification and labeling of the substance (when relevant), and a report of the conclusions from the risk assessment are thereafter forwarded to the Commission. This process is time limited – the authority must respond or complete the process within 30-60 days.

The Commission stores the submitted information on new chemicals in a database called the European list of notified substances (ELINCS) and publishes each year the full list of notified new substances in the Official Journal.

The regulation of existing substances. There are 100 116 substances registered in EINECS and thus regulated as "existing" chemicals. These chemicals represent about 99% of the total EU production volume (European Commission 2001).[6]

According to the existing substances regulations (Council regulation 793/93/EEC), these chemicals are to be risk assessed one by one according to the general principles laid down in Commission Regulation 1488/94. The chemicals are prioritized according to certain criteria which include (a) the effects of the substance on man or the environment (special attention shall be given to substances known or suspected to be carcinogenic, toxic to reproduction and/or mutagenic), (b) exposure, (c) data gaps, and (d) work carried out in other fora (article 8(2) of 793/93).

Each chemical to be risk assessed is assigned a "rapporteur", which is the competent authority in one of the member states. The member states volunteer to act as rapporteurs for individual substances. The rapporteur is responsible for gathering the available data and for providing a draft of the comprehensive risk assessment document. The draft risk assessment is thereafter discussed, and potentially revised, by the Technical Meeting on existing substances, and the (possibly modified) risk assessment conclusions are agreed upon. The result of the risk assessment is then forwarded to the Commission that can propose a strategy for risk reduction e.g. according to Council directive 76/769/EEG.

141 existing substances have been prioritized for risk assessment so far (Commission Regulations 1179/94, 2268/95, 143/97, and 2364/2000). For these substances base-set data are required according to the directive (article 9(2) of 793/93). For the substances not yet on the priority lists, no testing is however mandatory. This is a major problem with the existing substances' regulation that is reflected in the severe lack of toxicity data for existing chemicals.

Another important problem is the slow and resource consuming risk assessment process in which these substances are to be evaluated. Since 1993 draft risk assessments have been presented for 91 of the (more than 100 000) substances. The whole risk assessment and decision process is completed for 11 substances (of which 9 were assessed to be in need of risk reducing measures) (see the existing chemicals News Letter available at the home page of the European Chemicals Bureau (ecb.jrc.it/existing-chemicals)). Even if the speed of this process would increase so that decisions could be taken for as many as 20 substances a year it would still take another 5000 years before all the existing substances had been risk assessed. This is one of the

[6] EINECS does *not* include: synthetic polymers (which are registered in EINECS as their monomers), intentional mixtures, medical preparations, cosmetic preparations, pesticide preparations, food, feedstuff, alloys, most naturally occurring raw materials including coal and most ores (European Commission 2001).

reasons why proposals for new systems for data generation and risk assessment have been put forward.

3.3.3 Proposed new regulations for all general chemicals

A new strategy for a future chemicals policy outlined by the European Commission will lead to a single system – REACH – in which both existing and new substances will be subject to the same procedures (European Commission 2001). The REACH system will be composed of three elements: **R**egistration, **E**valuation and **A**uthorisation of **Ch**emicals.

According to the Commission proposition, registration of basic information will be required for the about 30 000 chemical substances marketed in the European Union in volumes exceeding 1 tonne (European Commission 2001). This information is to be submitted by the industry and registered in a central database.

Evaluation of the registered information will be required for the about 5000 substances exceeding a production volume of 100 tonnes per year. A "preliminary risk assessment" of these substances should be made by industry and further evaluation may be made by the authorities and will include priority setting for further testing.

Authorisation will be necessary for substances "with certain hazardous properties that give rise to very high concern" (European Commission 2001). The criteria for selection of substances to be subject to authorisation procedures remain to be established. Examples of candidate substance groups are substances classified as carcinogenic, mutagenic or toxic to reproduction (CMR) in categories 1 or 2, POPs (persistent organic pollutants), endocrine disrupting chemicals, PBT substances (persistent, bioaccumulating and toxic), and VPVB substances (very persistent and very bioaccumulating). The REACH proposal is still under discussion and the new regulations required for its implementation have not yet been agreed upon.

One of the purposes with this system is thus to increase the responsibilities for industry to perform testing of previously untested existing substances. For high-volume substances, comparatively extensive testing will be required, but for substances produced in lower volumes (1-10 tonne) only very basic (*in vitro*) testing will be mandatory, according to the current proposal, i.e. the testing requirements for existing chemicals will increase, while the requirements for new chemicals will decrease. Therefore, despite these initiatives, for most substances the data collected will be limited and significant gaps of knowledge will remain even after these data have been generated.

3.4 THE PRECAUTIONARY PRINCIPLE

According to the proposed Commission White Paper (Strategy for a Future Chemicals Policy) the European Commission aims at ensuring a high level of protection of human health and the environment and it is stated that the application of the precautionary principle is fundamental to achieving this objective:

> "Whenever reliable scientific evidence is available that a substance may have an adverse impact on human health and the environment but there is still scientific uncertainty about the precise nature or the magnitude of the potential damage, decision-making must be based on precaution in order to prevent damage to human health and the environment." (European Commission 2001)

A definition of the precautionary principle commonly advocated in Europe, is thus that on some occasions measures against a possible hazard should be taken even if the available evidence does not suffice to treat the existence of that hazard as a scientific fact (European Commission 2000b).

The precautionary principle has e.g. been criticized of marginalizing the role of science. However, according to the definition above, a rational decision-maker who applies the precautionary principle will use the same type of scientific evidence and assign the same weights to different data, as a decision-maker who requires full scientific evidence before regulatory actions are taken. The difference lies in the amount of such evidence that is required for a decision to act against a possible hazard. Therefore, the precautionary principle neither contradicts nor marginalizes science as a basis for decision-making (Sandin *et al* in press).

The precautionary principle is often interpreted as to be used by risk managers only and not in risk assessment (European Commission 2000a). Such a distinction requires that these two processes are separable. This is however not always the case. For example in the European classification regulations the processes of risk assessment and risk management are closely intertwined, since the result of the risk assessment, i.e. the classification, is directly connected to risk management decisions through down-stream regulations.

4 THE TRICHLOROETHYLENE CASE STUDY

To understand the complex regulatory process, close studies of the scientific basis and decision motivations must be undertaken. This thesis reports an in-depth investigation of 30 risk assessments performed of one and the same chemical substance – namely trichloroethylene (TCE).

4.1 AIMS AND HYPOTHESES OF THE PRESENT STUDY

The general purpose of the TCE case study is to increase the understanding of the regulatory process and of how risk assessments of chemicals are actually made.

A particular aim is to investigate to what extent risk assessors come to different conclusions, to describe the nature of these differences, and to discuss the reasons for them. The following factors was hypothesized to influence the overall conclusions of risk assessments: (1) what data were available (a time dependent factor), (2) what data were selected for evaluation, (3) how the data were interpreted, (4) how the scientific quality of individual studies was evaluated, and (5) the use of mechanistic data in animal to human extrapolation.

It is also the purpose of this study contribute to increase the understanding of how different risk assessors handle scientific uncertainty and to discuss how this may affect the outcome of the risk assessment.

The overall objective is to contribute to increase the transparency and reliability of risk assessments so that they better serve the needs of risk managers and the public.

4.2 BACKGROUND TO THE TCE CASE

TCE is a chlorinated solvent used in high volumes throughout the industrial part of the world. Its main current use is as an industrial solvent, but it has previously been used e.g. for medical purposes and for dry-cleaning. Several studies have reported tumors in various organs after TCE exposure, both in epidemiological studies and in rodent bioassays (mice and rats). The two most discussed tumor sites have been the liver and the kidneys. The toxicological evidence for these tumorigenic effects is briefly summarized below.

Liver tumors. The National Cancer Institute published the final report of the first TCE carcinogenicity bioassay in 1976 (NCI 1976). This study showed TCE to be carcinogenic in the B6C3F$_1$ mouse liver after oral exposure. The NCI study was however soon questioned since the TCE used was of technical grade and contained small amounts of potentially carcinogenic stabilizers that could have induced the carcinogenic response. Henschler *et al* (1984) performed a carcinogenicity bioassay on Swiss (ICR/HA) mice using TCE with and without the stabilizers. Oral administration of TCE with the stabilizers resulted in the induction of forestomach tumors in mice, and many risk assessors considered this to be a direct and local carcinogenic effect attributed to the stabilizers[7] (see Paper II). Exposure to pure TCE did not result in any significantly increased tumor incidence in this study, in the liver or elsewhere. (There was however a slight, non-significant, increase in liver tumors in all TCE-exposed groups of animals). Liver tumors in Swiss and B6C3F$_1$ mice after exposure to pure

[7] Epichlorohydrin or epoxybutane: Epichlorohydrine is classified by the IARC in category 2A, "probably carcinogenic to humans", and epoxybutane in category 2B, "possibly carcinogenic to humans" (www.iarc.fr 2000-06-17).

TCE were seen in the Maltoni *et al* (1986) inhalation experiments, and in the National Toxicology Program gavage study using $B6C3F_1$ mice (NTP 1990).

For a summary of the primary carcinogenicity data reporting mouse liver tumors see *Tables 2a-e* (Appendix).

Kidney tumors. Kidney tumors were first reported in male F344/N rats in a gavage study performed by National Toxicology Program in 1983 (NTP 1990). This study was criticized for the use of too high doses, since the TCE exposure resulted in pronounced toxicity in the kidney, and the survival rate of the rats was low. A subsequent National Toxicology Program gavage study using ACI, August, Marshall and Osborne-Mendel rats reported a statistically significant increase in renal tumour incidence in Osborne-Mendel rats, and a non-significant increase in "proliferative lesions" (hyperplasia, adenomas, and adenocarcinomas) in the ACI, August, and Marshall rats (NTP 1988). A non-significant increase in kidney tumours in rats was also seen in the studies published by Maltoni and co-workers in 1986 (Maltoni *et al* 1986). The relevance of these results was initially questioned because of the low incidences reported. The background incidence of renal tubular cell tumours in rats is however close to zero which makes even low increases in tumour incidence in treated rats toxicologically significant.

For a summary of the primary carcinogenicity data reporting rat kidney tumours see *Tables 3a-c* (Appendix).

Epidemiology. The early cohort studies (Axelson *et al* 1978 and Tola *et al* 1980) were negative. In subsequent studies, increased incidence ratios have however been reported for various organs and tissues. The main results of some of the key studies are as follows:

The results reported in Spirtas *et al* (1991), Axelson *et al* (1994), and Anttila *et al* (1995) individually, indicate no statistically significant increased cancer incidences. A meta-analysis indicates however an increased risk of liver and biliary tract cancers as well as non-Hodgkin's lymphoma (IARC 1995).

The results reported in Henschler *et al* (1995) and Vamvakas *et al* (1998) indicate an increased risk of renal cancer after high to very high occupational exposure to TCE. The study by Brauch *et al* (1999) reported a correlation between TCE exposure, renal cell carcinoma, and specific mutations in the von Hippel-Lindau (VHL) tumour suppressor gene, which indicates that TCE exposure is associated with specific mutations in the human kidney.

Generally speaking, inconsistent results, small increases in the incidence ratios, design weaknesses, and uncertainty about the validity of the data reported in some of these studies make the interpretation of the TCE epidemiological data difficult, and the conclusions uncertain. For a summary of these epidemiological data see *Table 4* (Appendix).

4.3 MATERIALS AND METHOD

The carcinogenicity of TCE has been selected as model for this study since it has a large primary database compared to other existing substances and since a large number of risk assessments of TCE (discussing carcinogenic effects) have been performed by different expert groups in Europe, USA and Canada. National organizations (such as the Swedish Institute of Environmental Medicine) and international organizations (such as WHO, IARC, and the European Commission), as well as joint groups of agency, industry and academic representatives (such as the ACGIH), are represented.

The TCE risk assessment documents were identified by using the Riskline, Medline and Toxline databases, by personal communication with knowledgeable persons, and by utilizing the reference lists of the retrieved risk assessment documents. The selection was limited to documents available in the English, German, or any Nordic language, and the objective was to cover as many of these risk assessments as possible (review articles are not included). 30 documents, published between 1973 and 2001 were identified in this way. The TCE risk assessment documents are listed separately in the list of references.

In the first part of the TCE case study, detailed information from 29 TCE risk assessments (published at that time) was stored in a database, using "Access" software. This database is from now on referred to as the TCE database. The information gathered in the TCE database includes:

1. *The type of organization that was responsible for the risk assessment* (academic, government, agency, industry, international organization, or mixed group with academic, government, and industry representatives.)
2. *The identity (bibliographic reference) of each study/experiment used in the section describing and interpreting carcinogenicity bioassays and epidemiology and in the conclusion (summary/discussion) section.* This information made it possible to compare the risk assessments in terms of their coverage of primary carcinogenicity data.
3. For each study/experiment utilized by the risk assessors in the section describing and interpreting carcinogenicity bioassays and epidemiology: *How the quality of the study was assessed*, i.e. if it was described by the risk assessors as adequate, inadequate, or reasonable, or if the quality of the study was not commented on. In the cases when the evaluation made by the risk assessor was implicit rather than explicit, my interpretation of the implicit evaluation was recorded in the database. (This information was stored with the intention to compare how different risk assessors evaluated one and the same experiment or epidemiological study.)
4. For each study/experiment discussed in the section describing and interpreting carcinogenicity bioassays and epidemiology: *How the results of the study/experiment were interpreted*, i.e. whether this study was considered to suggest, or used as an argument in favor of, a carcinogenic effect caused by TCE exposure (positive results), or as an argument for the absence of a carcinogenic potential (negative results), or the study was considered inconclusive for the purpose of evaluating carcinogenic potential, or this was not commented on. In some cases when the conclusion drawn by the risk assessor was implicitly rather than explicitly stated, my interpretation of the implicit statement was recorded in the database. (This information made it possible to compare how different risk assessors interpreted the results of one and the same experiment or epidemiological study.)
5. *The hypotheses presented by the risk assessors concerning carcinogenic mechanisms of TCE and their relevance to humans as well as the identity of the primary data that were used to substantiate these hypotheses.* This information was used to compare how different risk assessors use mechanistic data. The use of mechanistic data in carcinogen risk assessment is an issue of current interest that involves significant scientific uncertainty and the study of this practice is therefore useful for elucidating different ways of handling scientific uncertainty.

6. *The general conclusions drawn in the risk assessment document* on (i) TCE carcinogenic potential in animals (as indicated by bioassays), (ii) TCE carcinogenic potential as indicated by epidemiological studies, and (iii) overall human cancer risk. In cases when explicit statements about these three conclusions were not provided in the risk assessment documents, my interpretation of the available statements were recorded in the database.

For a more thorough description of the TCE database, see Paper I.

The first task of this study was to describe and compare the different conclusions drawn in the TCE risk assessments. Since there is no established method available for this kind of comparison, a method was constructed in the form of a carcinogen risk assessment index (CRAI). In order to compare risk assessments with different scopes and purposes, the focus was put on a basic issue that was treated in all of them, namely on the part of the risk assessment devoted to hazard identification and the conclusions on whether or not there is enough evidence that the substance has a carcinogenic effect.

The proposed CRAI has three parameters. The first parameter describes the conclusion on animal carcinogenicity based on animal data. If the risk assessor considers the substance to be carcinogenic in animals (a possible, a probable or a proven carcinogen) the first parameter of the index is "+". If the risk assessor does not consider the substance to be an animal carcinogen, or if this is not commented on, then it receives the index value "–".

The second parameter refers to the conclusions drawn from epidemiology. If epidemiology is considered by the risk assessor to be positive, then the index "+" is assigned. If the risk assessor considers epidemiology to be negative, or if this is not commented on, then a "–" is assigned.

The third parameter describes the overall conclusion on "human cancer risk". Its value will be "+" if the conclusion drawn by the risk assessors gives an indication of a (possible or probable) human cancer risk. If a cancer risk to humans is described by the risk assessors as implausible, or if the human cancer risk is not commented on at all, then this part of the index will be "–".

The carcinogenicity risk assessment index has a theoretic maximum of eight groups, but all the TCE risk assessments belonged to the following groups:

1) – – – (Not carcinogenic in animals, negative epidemiology, no/implausible human cancer risk).[8]

2) + – – (Carcinogenic in animals, negative epidemiology, no/implausible human cancer risk).[9]

[8] This category was assigned if the risk assessors have concluded that TCE has not been shown to be carcinogenic in animals (or if a carcinogenic effect seen in animal bioassays is not considered to be a direct effect of the TCE exposure). Regarding epidemiology, they either said that no conclusion can be drawn because of insufficient data or that on the basis of existing epidemiological data, TCE is considered not to be a human carcinogen.

[9] This category was assigned if the risk assessors made an explicit statement that TCE is carcinogenic in at least one animal species. Regarding epidemiology, they either said that no conclusion can be drawn because of insufficient data or that on the basis of existing epidemiological data, TCE is considered not to be a human carcinogen.

3) + – + (Carcinogenic in animals, negative epidemiology, a plausible human cancer risk).[10]

4) + + + (Carcinogenic in animals, positive epidemiology, a plausible human cancer risk).[11]

In the second part of the TCE case study the use and interpretation of primary data in the most recent risk assessment document (UK 2001), and in the process of classification and labeling of TCE according to the European Union regulations were studied. This part of the study was performed by analysing the minutes from the meetings of national and other experts in the process of classifying TCE according to the European Union regulations.

4.4 RESULTS AND DISCUSSION

4.4.1 Paper I

CRAI categorization. The categorization of the TCE risk assessment documents according to the CRAI shows that the risk assessors have come to divergent estimates of the TCE potential to cause cancer. The 29 TCE risk assessment documents belong to four different CRAI groups; Six were categorized in the – – – group, ten in the + – – group, nine in the + – + group, and finally four documents in the + + + group (*Table 5*).

[10] This category was assigned if the risk assessors made an explicit statement that TCE is carcinogenic in at least one animal species, and that TCE is not considered a carcinogen on the basis of epidemiology, and that a human cancer risk is still considered plausible in the overall conclusions.

[11] This category was assigned if the risk assessors explicitly concluded that TCE is an animal carcinogen, and that epidemiological evidence indicates that TCE is a human carcinogen.

TABLE 5. *The categorization of the TCE risk assessment documents according to the CRAI.**

– – –	+ – –	+ – +	+ + +
• NIOSH (1973) USA.	• IARC (1976).	• NIOSH (1978), USA.	• Inst of Env Medicine, (1990) Sweden.
• Health and Safety Executive (1982), UK.	• IARC (1979).	• Nordic Expert Group (1979).	• IARC (1995).
• VROM (1984) The Netherlands.	• NBOSH (1981), Sweden.	• EPA (1985)	• DFG (1996), Germany.
• ACGIH (1989), USA.	• WHO (1985).	• Inst of Env Medicine (1986), Sweden.	• MAK (1996) Germany.
• ACGIH (1992), USA.	• IARC (1987).	• EPA (1988), USA.	
• ACGIH (1996), USA.	• CEC (1990).	• ATSDR and EPA (1989), USA.	
	• Nordic Expert Group (1991).	• Canadian EPA (1993), Canada.	
	• ECETOC (1994).	• OECD/EU (1996), (UK).**	
	• GDCh (1994), Germany.	• ATSDR (1997), USA.	
	• HSIA (1996).		

* The CRAI has four different groups:
– – – (Not carcinogenic in animals, neg. epidemiology, no/negligible human cancer risk),
+ – – (Carcinogenic in animals, negative epidemiology, no/negligible human risk),
+ – + (Carcinogenic in animals, negative epidemiology, a possible, non-negligible, human cancer risk),
+ + + (Carcinogenic in animals, positive epidemiology, a non-negligible human cancer risk).

** This is the draft of the comprehensive Existing substances risk assessment document made within the European Union (cited with permission from the Health and Safety Executive). The final version of this document was published in 2001 (UK 2001). This document was not available when this categorization was made.

There is no standardized way for risk assessors to present their overall conclusions. Categorizing the risk assessments according to the CRAI was in some cases complicated due to difficulties in understanding the exact meaning of the conclusions as the different risk assessors presented them. For a more detailed description of the CRAI categorization, see paper I.

Data availability. The publication dates for the TCE risk assessments in the different CRAI groups were quite evenly distributed (except for the + + + group, in which all the risk assessment documents are published relatively late i.e. in the 1990s). This raised questions about the influence that data availability (a time dependent factor) have had on the risk assessment conclusions. To examine the impact that new scientific data may have on the risk assessment conclusions, the arguments used in the different documents to justify their overall conclusions were analyzed in terms of their openness to revision by the generation of new data.

This analysis showed that the risk assessors in the – – – group use four different arguments for their conclusion, namely (1) Carcinogenicity data is lacking (implicit; carcinogenic potential is not discussed) (NIOSH 1973). (2) The results reported in the early bioassays are confounded because the TCE used contained carcinogenic stabilizers (HSE 1982). (3) Mouse liver tumours alone are of low relevance for risk assessment (VROM 1984), and, (4) the bioassay results are confounded by the use of too high doses that resulted in organ toxicity (ACGIH 1989, 1996).

The first three of these arguments are put forward in risk assessment documents published relatively early (1973, 1982 and 1984), and these arguments have subsequently been affected by the publication of new scientific data. (I.e. after the first carcinogenicity studies were performed and the results were published, experiments were performed with pure TCE, and tumors were also seen also in mouse lung and rat liver).

The fourth argument however (questioning the relevance of carcinogenicity bioassays using high doses) is not TCE specific and refers to a general discussion about the relevance of the use of doses near or at the "maximum tolerated dose" for carcinogenicity testing (see e.g. Ames and Gold 1990, and Huff 1993). This argument is science based, since it includes considerations of toxicological thresholds and the saturation of metabolic pathways, but it also has non-scientific components since the design of toxicity studies in practice has to be based on a tradeoff between e.g. the predictive power of the study and the cost of performing it.

The publication dates for the + – – group range from 1976 to 1996. For this group two main motivations are given. The first is that the available scientific evidence is insufficient for considering TCE to be a human carcinogen (IARC 1976, 1978, and 1987, NBOSH 1981, WHO 1985, NEG 1991, CEC 1990, and GDCh 1994). The second is that the carcinogenic mechanism is sufficiently known and that it has been found to be irrelevant to humans (ECETOC 1994, HSIA 1996). The first of these two arguments is certainly open to correction by increasing knowledge. The second argument does however not call for more knowledge, and thus seems less open to revision.

The publication dates for the + – + group range from 1978 to 1997. (This is similar to the + – – group). In the + – + group, uncertainty in the scientific data is stressed, and the conclusion that TCE may pose a carcinogenic hazard to man can generally be described as based on precaution. This type of cautious argumentation is thus open for revision by further knowledge, and increased knowledge could both increase and decrease their estimate of the carcinogenic hazard.

The risk assessment documents in the + + + group are all published relatively late, i.e. in the 1990s. The conclusions drawn by the DFG (1996) and the IARC (1995) are motivated by the interpretation of data obtained from epidemiological studies published in 1995 and thereafter. The conclusion drawn by the IMM in 1990 was on the other hand based on less scientific knowledge and is thus to a higher extent based on a cautious interpretation of the data available at the time.

Data selection. Ideally, risk assessors should concur to a large degree on what data are relevant to the assessment. Furthermore, one might expect them to quote all the relevant references available to them; high reference coverage was therefore expected. This hypothesis was however not confirmed.

From the detailed information in the TCE database about all references used in the sections of the risk assessment documents evaluating carcinogenicity data, the *reference coverage* for each of the documents was calculated. The reference coverage is defined as *the percentage of the total number of available scientific references that the risk assessment document cites (cited references / available references*). This calculation suggests that the data sets on which some of the TCE risk assessments are based are surprisingly incomplete and diverse. The average total reference coverage for 29 risk assessment documents was only 18%. Furthermore, 151 of the 259 references in the database (58%) were cited only once, i.e. by only one risk assessor.

There are different reasons for low (total) reference coverage. The five lowest values for reference coverage (i.e. NBOSH (1981), ACGIH (1989), ACGIH (1992), ACGIH (1996), and NEG (1979)) are due to the fact that the reference lists for these documents were not up-to-date. This could happen e.g. if there is for some reason a long time lag between data collection and publication of the risk assessment document. For ACGIH however, the list of carcinogenicity bioassay references had not changed from 1989 to 1996; The carcinogenicity bioassay data (as selected in this subsample) are therefore the same in the three ACGIH documents published in 1989, 1992 and in 1996.

For the other risk assessment documents with low reference coverage (DFG/MAK 1996, OECD/EU 1996 and CEC 1990) the low coverage has another reason. These risk assessors have included newer data, but they have also excluded some of the oldest bioassay references. This results in a lower coverage of this subsample of references.

There may however still be a core of important data for which reference coverage is high. Obvious candidates are long-term/carcinogenicity studies on animals, since such studies are potentially significant contributions to a risk assessment. It may therefore be expected that the risk assessments cover a near one hundred percent of these studies. Nine of the studies in the TCE database included the word "long-term-", "chronic-", "carcinogenicity-", or "carcinogenesis-" study in their title. (Unpublished or preliminary data, and secondary sources were excluded). These nine studies contain fourteen experiments.[12] The reference coverage of these experiments varied from 29 to 100% for the different risk assessment documents. The average coverage was 78%, and the median coverage was 86% (see *Table 6A*). Although this is higher than for all references, the minimum is still far from 100%.

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[12] NCI 1976 (two experiments) ; Henschler *et al* 1984 (one experiment) ; Van Duuren *et al* 1979 (two experiments); Henschler *et al* 1980 (three experiments); Fukuda *et al* 1983 (two experiments); Maltoni *et al* 1986+1988 (two species, one record) ; NTP 1988 (Technical Report 273) (one species); NTP 1982-1990, Technical Report 243 (two experiments).

TABLE 6A. *Risk assessment documents' reference coverage of 14 carcinogenicity bioassay experiments.*

Risk assessment document	Reference coverage (%)	(Cited / available)
NEG/NBOSH 1979+1981	29	(2/7)
ACGIH 1989	50	(7/14)
ACGIH 1992	50	(7/14)
ACGIH 1996	50	(7/14)
NEG 1979	50	(2/4)
DFG/MAK 1996	57	(8/14)
OECD/EU 1996	57	(8/14)
HSIA 1996	71	(10/14)
VROM 1984	73	(8/11)
EPA 1985	75	(9/12)
CEC 1990	79	(11/14)
NEG 1991	86	(12/14)
CEPA 1993	86	(12/14)
EPA 1985+1988	86	(12/14)
IARC 1976+1979+1987	86	(12/14)
IMM 1986	92	(11/12)
GDCh 1994	93	(13/14)
ATSDR 1997	93	(13/14)
NIOSH 1978	100	(2/2)
IARC 1979	100	(2/2)
HSE 1982	100	(7/7)
ATSDR/EPA 1989	100	(14/14)
IMM 1986+1990	100	(14/14)
ECETOC 1994	100	(14/14)
IARC 1995	100	(14/14)
WHO 1985	100	(12/12)

Another group of studies for which high reference coverage should be expected is the epidemiological studies. The epidemiological references were selected that had been assessed by at least one risk assessor to be adequately designed and performed. This resulted in a subsample of eight studies.[13] For this subsample, reference coverage varied from 38 to 133 percent[14] (average 72%, median 67%), so the reference coverage minimum for epidemiology was also low (see *Table 6B*).

[13] Anttila *et al* (1995); Axelson *et al* (1978); Axelson *et al* (1984); Axelson *et al* (1994); Heineman *et al* (1994); Henschler *et al* (1995); Spirtas *et al* (1991); Tola *et al* (1980).

[14] The IARC refers to two epidemiological studies published in the same year as the risk assessment document (1995), i.e. Anttila *et al* (1995) and Henschler *et al* (1995). According to the standardized definition of availability adopted for the purpose of this paper, these studies were not available to them, therefore references coverage exceeds 100 per cent in this case.

TABLE 6B. *Risk assessments' reference coverage of 8 epidemiological studies, each of which at least one risk assessor has considered adequately designed and performed, according to the records in the database.*

Risk assessment document	Reference Coverage (%)	Cited/available
NIOSH 1973	n.a.	(0/0)
IARC 1976	n.a.	(0/0)
NIOSH 1978	n.a.	(0/0)
HSIA 1996	38	(3/8)
ACGIH 1996	38	(3/8)
NEG/NBOSH 1979+1981	50	(1/2)
CEPA 1993	50	(2/4)
GDCh 1994	50	(2/4)
MAK 1996	63	(5/8)
EPA 1985	67	(2/3)
IMM 1986	67	(2/3)
EPA 1985+1988	67	(2/3)
ATSDR/EPA 1989	67	(2/3)
ACGIH 1989	67	(2/3)
CEC 1990	67	(2/3)
NEG 1991	67	(2/3)
IARC 1976+1979+1987	67	(2/3)
ACGIH 1992	75	(3/4)
DFG 1996	75	(6/8)
ATSDR 1997	75	(6/8)
OECD/EU 1996	88	(7/8)
IARC 1979	100	(1/1)
NEG 1979	100	(1/1)
HSE 1982	100	(2/2)
VROM 1984	100	(2/2)
WHO 1985	100	(3/3)
IMM 1990	100	(3/3)
ECETOC 1994	100	(4/4)
IARC 1995	133*	(8/6)

*See footnote 14.

In spite of the low total reference coverage, there might still be individual important studies that are cited by many risk assessors. To test this, focus was changed from the risk assessment documents to the primary data publications, and the *citation coverage* was calculated. The citation coverage of a particular study is defined as *the percentage of the risk assessment documents, to which the study was available, that cite it.* Examples of especially important studies could most likely be found among a subsample of the long-term bioassays. The citation coverage for the 14 available long-term experiments varied from 59 to 96%, with an average of 80% (median 77%). No single carcinogenicity study reached a hundred per cent citation coverage.

In a subsample of eight epidemiological studies (selected on the basis of how their quality was evaluated by the TCE risk assessors) the citation coverage varied from 19 to 91% with an average of 66%, and a median of 75 %. No single epidemiological study reached a hundred percent citation coverage.

The analysis of reference coverage indicates that some of the risk assessors have used data sets that are "biased" towards either positive or negative studies. In some cases this bias correlates to the risk assessment's overall conclusions (see also Rudén, manuscript).

Data quality evaluation. By evaluating the scientific quality of a study, the weight that this study is given in the overall risk assessment is determined. High quality studies are more valuable contributions to the risk assessment than studies of inferior quality, and thus they should be more influential.

There are 259 records of different primary data in the database. These 259 references (studies or experiments) are cited a total of 790 times in the 29 TCE risk assessments. In 515 (65%) of these 790 citations the risk assessors make no comment on how they evaluate the quality of the study. Hence, in most cases nothing is said about the quality of study design and conduct. Even though it is a central issue in risk assessment, the process of quality evaluation is thus far from transparent.

4.4.2 Paper II

Interpretation of bioassays. The interpretation of individual primary bioassay data for risk assessment purposes includes at least two components. First, an assessment of the actual results obtained in the specific study or experiment has to be made. This is in part a matter of assessing statistics attempting to answer the question whether there is a positive carcinogenic response in the experiment or not.

Secondly, the relevance of the results is assessed. This part of the interpretation process should provide an answer to the question whether the response seen in the bioassay is causally connected to the exposure of interest, or if the results could be confounded e.g. by differences in the composition of the test substance which actually caused the carcinogenic response, or by viral infections increasing the incidences of lymphomas (as in the TCE example described in paper IV).

The relevance could also be assessed at the level of human cancer risk, i.e. to determin if the data are relevant to the human health risk assessment. The assessment of toxicological relevance is often closely connected to, and sometimes difficult to distinguish from, an assessment of scientific quality. The relevance assessment (as well as data quality assessments) is often implicit, which makes this process less transparent.

About one fourth of the primary carcinogenicity data (bioassays and epidemiological studies) referred to in the TCE database were interpreted differently by different risk assessors. The main differences in the interpretations of bioassays were either different assessments of statistics or different assessments of the toxicological relevance of the results obtained.

Regarding the assessment of statistics, there were differences in the preferred statistical method of analysis and in how statistically non-significant effects were assessed and communicated.

Regarding the assessment of toxicological relevance of the bioassay results, one example is identified in which a particular risk assessor (the IARC) assessed the relevance of primary data results differently than other risk assessors and differently than the authors of the original paper. There are also examples of when risk assessors have changed their interpretation of particular primary data in the light of new data,

changes that in these examples also correlated to a change in their overall risk assessment conclusions.

Interpretation of epidemiological data. In studying the interpretation of epidemiology, the key epidemiological studies were identified, and the use and interpretation of these data were compared for the three TCE risk assessors that have considered epidemiology to be positive (i.e. IARC 1995, DFG/MAK 1996, and IMM 1990), and four contemporary risk assessors (ACGIH 1996, HSIA 1996, OECD/EU 1996 and ATSDR 1997) concluding that epidemiology is negative.

This analysis showed that the three risk assessors concluding that epidemiology is positive base their conclusion on different studies, reporting carcinogenic effects in different organs. The IARC classification of TCE as a "probable human carcinogen" is mainly based on a meta-analysis of the results reported in three epidemiological studies; Spirtas *et al* (1991), Axelson *et al* (1994), and Anttila *et al* (1995) (together with the data on animals which were considered to be "sufficient"). The results in these epidemiological studies taken individually indicate no significant increased incidences. The meta-analysis however show an increased relative risk of cancer of the liver and biliary tract (IARC 1995, p. 135).

DFG (1996) motivates the conclusions by assigning more weight to the data from Germany reported by Henschler *et al* (1995) than the other TCE risk assessors, while the IMM (1990) refers mainly to the Swedish epidemiology available at the time that reports increased incidences of tumors in the hematolymphatic system and the urinary tract (Axelson *et al* 1986). The IMM finds these data to be inconclusive, but when taken together with bioassay results, it may still, according to the IMM indicate a positive response. The IMM thus base their conclusion on a cautious interpretation and extrapolation of less data. (It could be noted that in this example the German risk assessors assigned more weight to the German epidemiology, and the Swedish risk assessors assigned more weight to the Swedish epidemiology.)

The four contemporary risk assessors concluding that the TCE epidemiology is negative motivate their decision with the following arguments: (1) the majority of the epidemiological data are negative, and (2) the positive data are insufficient due to lack of consistent findings, limited statistical significance, or questionable quality. None of these four risk assessors has utilized the meta-analysis performed by the IARC, and none of them considers the German data to be conclusive.

4.4.3 Paper III

Scientific knowledge about mechanisms of chemically induced carcinogenesis has increased, and mechanistic data are becoming more influential as arguments in the risk assessments of chemicals (IARC 1992). However, the question of how much evidence is needed for considering a carcinogenic mechanism scientifically proven is an issue that involves both scientific and policy considerations.

In paper III the handling of scientific uncertainty related to mechanistic hypotheses is analyzed and it is investigated how this uncertainty affected the outcome of the risk assessment. This is done by comparing the use and interpretation of mechanistic data in two reasonably contemporary risk assessments, namely the ECETOC (1994) and the OECD/EU (1996) risk assessments.

The analysis shows that in the TCE case these risk assessors differed in the amount of evidence that they require for considering a carcinogenic mechanism to be scientifically plausible. In this example, the OECD/EU risk assessors require more data than do the ECETOC to conclude that the mouse lung tumors are probably

irrelevant to humans. There are also differences in the ways that these risk assessors interpret individual primary data (differences that correspond to the different overall risk assessment conclusions drawn).

The results of this study also indicate that the criteria for selecting primary data do not solely depend on considerations regarding experimental design and predictive power. In this example, this is reflected in the use of studies being inadequate for drawing conclusions about carcinogenic potential, as indicating the absence of such a potential.

There is in this material also an interesting example of different choice of sources. The ECETOC on one occasion cites an unpublished industry report, while the OECD/EU cites a paper from the open literature and on the basis of these two papers they draw different conclusions regarding the relative importance of two metabolic pathways in humans.

4.4.4 Paper IV

Since the results reported in the first three manuscripts suggested that the selection of data in the 29 TCE risk assessment documents are diverse, a study of the risk assessment process in a setting where different risk assessors had access to exactly the same database was motivated. This criterion is satisfied in the European Union regulatory process for TCE within the classification and labeling process.

In paper IV the classification made of the TCE in 1976, and the two subsequent revisions of this classification (in 1988 and 2000) are scrutinized. Carcinogenic substances can be classified in three different categories depending on the degree of evidence for carcinogenicity that is available. This study was performed by comparing the classification criteria to the primary data on TCE carcinogenicity that were available at the points in time when the TCE classification has been made or revised (1976, 1988 and in 2000). Both the criteria in force at the time of the revisions, as well as the criteria currently in force are used for the comparison.

On the basis of this analysis, I argue that in 1976, when TCE was classified as "harmful", the TCE database could have been interpreted to fulfill both the current and the 1976 requirements for classification as a category 3 carcinogen. In 1988, when TCE was classified as a category 3 carcinogen, its database could have been interpreted to fulfill both the current and the 1988 requirements for a classification as a category 2 carcinogen, and when TCE recently was classified as a category 2 carcinogen, it could be argued that on the basis of the available data that it was also possible to classify it in category 1 for carcinogenicity. Hence, it would have been possible to strengthen all these three classifications and the assessments made would still be in line with the classification criteria (both the criteria in force at the time of these classifications, and the ones currently in force).

In the European classification and labelling regulations the process of risk assessment and that of risk management are not separable. As specified in the legislation, the result of the risk assessment has direct implications for risk management decisions since the classification of substances into certain danger classes (e.g. carcinogenic or mutagenic or toxic to reproduction in the two strictest categories) automatically results in risk reducing measures (substances classified in these categories may e.g. not be sold to the general public).

According to the Commission White Paper (European Commission 2001) the precautionary principle urges us to undertake risk-reducing measures even in the absence of full scientific knowledge, in order to prevent damage to human health and the environment. Therefore it is concluded that, to the extent that the classifications of TCE are representative of the process as a whole, the need for a revision of the current practices in the classification and labelling process might be a subject for

discussions in the light of the objectives set out by the Commission for the future European chemicals control.

4.4.5 Paper V

In paper V the controversies within the classification and labeling process are identified. This study was performed by scrutinizing the minutes from the meetings of national and other experts in the process of classifying trichloroethylene (TCE) according to the European Union regulations. The primary carcinogenicity and epidemiological data that these experts refer to as well as the documents submitted to these meetings by different participants are also analysed.

The European regulatory process for the classification and labeling of chemical substances can be divided into three consecutive parts: the technical process, the decision process, and the implementation process. In the technical process toxicological experts discuss the toxicological data and apply the classification criteria to come up with a proposal for appropriate classifications of individual substances. After this, the formal decision is taken by the European Commission. (The decisions are usually taken for large groups of substances at a time – up to 400 substances). The decision is finally forwarded to the Technical Progress Committee that implements the decision. The focus of this study is on the technical part of the regulatory process. This part of the process has the following main participants:

The Technical Meeting on Existing Substances following Council Regulation (EEC) 793/93. This group consists of representatives from the Commission, from the competent authorities in the member states (national experts), and from industry. The size of this group varies since member states and industry send their experts on a voluntary basis, but it can be as large as 70-80 representatives. Industry sometimes accounts for as much as half of the total number of experts.

The Commission Working Group on the Classification and Labeling of Dangerous Substances. This group is also loosely put together since it is voluntary for member states to send representatives and since they send different experts to different meetings depending on the substances and particular issues that are to be discussed. The representatives come from the competent authorities in the member states, and from industry. The size of the group is about 30-40 representatives.

The Commission Group of Specialised Experts in the fields of Carcinogenicity, Mutagenicity and Reprotoxicity consists of experts selected by the competent authorities in the different member states (one or two experts per member state). The participants of this group differ depending on which issues and substances are to be discussed. Industry is never formally represented in the group of Specialised Experts, but they sometimes have the opportunity to present their views to the group.

In this paper it is shown that within this process there are disagreements between the actors that were most active and influential in the TCE case (namely the experts from United Kingdom, Sweden, Germany, and from industry) about which is the appropriate classification of mutagenicity (no classification or category 3) and of carcinogenicity (categories 1, 2, or 3). These disagreements were maintained, or even accentuated, during the 4-year process. This illustrates the relatively wide scope of conclusions that can be drawn from different interpretations of the data set in the application of the classification criteria.

Underlying the different opinions among member state and other experts regarding the appropriate classification for mutagenicity and carcinogenicity were disagreements about (1) the handling of conflicting data, (2) how to handle lack of data, and (3) how to evaluate data obtained from non-validated methods.

Conflicting data. The weight that individual bioassay data are given in the risk assessment process depends on how the quality and relevance of these data are assessed. If there are conflicting data that have similar quality and relevance, it is cautious (health protective) to give more weight to the positive data than to the negative. In the TCE case, the Swedish experts and the Commission Specialised Experts were among those participants who made a more cautious interpretation of the conflicting bioassay data.

The TCE epidemiological data set also contains conflicting observations. In this case, the German and the Swedish risk assessors lie on the more health protective side of the interpretation range (suggesting a category 1 classification), the Commission Specialised Experts are in between (suggesting a category 2 classification), and the UK risk assessors and industry are at the less health protective part of the interpretation range (advocating a category 3 classification).

Lack of data. New scientific data evolve continuously, and in that sense, all regulatory measures are provisional and may be revised in the face of new information. In risk management the disadvantages of overregulating a substance must be weighed against the disadvantages of underregulating a substance.

The TCE mutagenicity data were assessed by the Specialised Experts in 1997 to be insufficient for classifying TCE as a mutagenic substance, but the available data raised concern and warranted further testing which was requested under the regulations.

In response to this, a majority of the participating national experts voted to halt the classification process while awaiting the requested mutagenicity data. No provisional classification for mutagenicity or carcinogenicity was assigned to TCE during this (15 months) period.

Non-validated experimental methods. Data obtained from newly developed (non-validated) experimental methods can supply important information to a risk assessment. The relevance of data obtained from non-standardized tests, or modified guideline assays, are however uncertain. Each experiment's strengths and weaknesses must therefore be evaluated on a case-by-case basis.

Statements from UK and Swedish experts indicate that there exists a general difference in how positive data from non-validated tests and negative data from such tests are evaluated. Negative results obtained from non-validated experimental methods are usually not accepted by the member state experts, while positive data are. The UK, and some of the Specialised Experts argued however that positive non-validated data should be given the same weight as negative non-validated data.

4.5 CONCLUDING REMARKS

The TCE database contains more than 14 long-term carcinogenicity experiments. Long-term bioassays have been performed with three different species (mouse, rat and hamster) and by all the relevant exposure routes (oral, inhalation and dermal). Furthermore, at least eight epidemiological studies of reasonable to high quality are available. This is a huge amount of data compared to what is available for the average existing substance and compared to what is currently required for the notification of new substances, as well as the test requirements proposed in REACH. The TCE data set is thus not representative for existing substances in general. The size of the data set and the number of TCE risk assessments is remarkable considering the large number of chemical substances that lack important data and have yet never been risk assessed. Such extensive testing and assessment of individual substances is not

feasible for the majority of substances but is sometimes motivated, e.g. for chemicals that pose significant health risks and for substances of great economic importance.

The risk assessors under study come to divergent conclusions about the TCE potential to cause cancer. There is however no general time trend in these differences, which indicates that the different conclusions cannot exclusively be explained by a developing database. Differences between these risk assessors are identified in how they select, interpret and evaluate individual primary data (bioassays, epidemiological and mechanistic data). These differences are all considered to be within the scope of the scientifically acceptable.

There is always uncertainty inherent in toxicological data. The uncertainty exists to some extent at the primary data level, i.e. scientific uncertainty inherent in the toxicological study methods, and to a greater extent at the level of the data set and in the extrapolation and interpretation of, sometimes conflicting, data. This uncertainty opens up a scope of possible interpretations. The major challenge for a risk assessor is to make a scientifically based assessment of these uncertainties, and to evaluate and handle them in order to present a scientifically defensible and robust risk assessment.

Differences in the assessment and handling of scientific uncertainty can affect more than one part of the risk assessment process (i.e. data selection, data interpretation, quality evaluation of individual primary data, and extrapolations) and thus have the potential to affect the overall conclusions. Such differences will however not be apparent to the readers of a risk assessment document unless they are familiar with the primary data set, or risk assessment documents of one and the same substance that differ in these respects are carefully compared. The scope of possible conclusions is seldom transparently described in risk assessment documents (by e.g. an interval) and the arguments for reducing or acknowledging scientific uncertainty are often implicit.

The results from the TCE case study suggests that even if an enormous amount of resources are spent on testing of individual substances, significant uncertainty about their potential to cause harm may still remain. In fact, uncertainty may even increase with the generation of new data since the net result of further research may (for quite a while) be that further hypotheses are proposed rather than that the original hypothesis is being corroborated or falsified. Scientific uncertainty in risk assessment of chemicals can thus only partly be eliminated by data generation. Therefore there is an urgent need for methods to make preliminary and precautionary risk assessments of chemicals on the basis of incomplete knowledge.

Further efforts should be made to improve the analysis and description of scientific uncertainty, and the strategy used for handling scientific uncertainty should also be clearly accounted for in order to make toxicological risk assessments more transparent and reliable as a basis for risk management decisions. Such practices would facilitate a structured, science based application of the precautionary principle in risk management.

APPENDIX

In the following tables some of the experimental and epidemiological data on TCE are briefly summarized. The purpose of this appendix is to give a (very crude) picture of the available data set.

TABLE 2 (a-e). *Summary of primary data – liver carcinogenicity (mice)*

a. NCI 1976

TCE purity: >99% pure (containing epichlorohydrin)
Strain and species: B6C3F$_1$ mice
Route of exposure: oral gavage
Duration of exposure: 5 times per week for 78 weeks
Duration of experiment: 90 weeks
No of animals: 50 + 50 per dose group
Vehicle: corn oil

	Male			Female		
Dose (mg/kg)	0	1169	2339	0	869	1739
Incidence (hepatocellular carcinoma)	1/20	26/50 ($p<0.01$)	31/48 ($p<0.01$)	0/20	4/50 ($p=0.09$)	11/47 ($p<0.01$)

b. Henschler *et al* 1984

Strain and species: Swiss (ICR/HA) mice
Route of exposure: oral gavage
Duration of exposure: 5 times per week for 78 weeks
Duration of experiment: 106 weeks (animals observed during their total lifespan)
No of animals: 50 + 50 per group
Vehicle: corn oil

EPC = Epichlorohydrin
BO = Epoxybutane
% = w/w
TCE doses: 2400 mg/kg (Male) or 1800 mg/kg (Female)

	Vehicle control	Pure TCE	Industrial Grade TCE	TCE+ 0.8%EPC	TCE+ 0.8%BO	TCE+ 0.25%EPC+ 0.25%BO
Total number of liver and biliary tract tumors (Male/Female)	5/1	8/3	10/3	4/3	4/3	7/5
"Comparison of X^2-values, not age adjusted, for hepatocellular adenomas and carcinomas and preneoplastic nodules of the liver in exposure groups and control." (Male/Female)		(p=0.29 / >0.05)	(p=0.06 / p>0.05)	(p=1.0 / p>0.05)	(p=0.69 / p>0.05)	(p=0.29 / p>0.05)

Source: Henschler *et al* 1984, table 5 and table 8.

c + d. Maltoni *et al* 1986

TCE purity: Epichlorohydrin-free
Strain and species: Swiss mice
Route of exposure: Inhalation
Duration of exposure: 7 hours, 5 days per week for 78 weeks
Duration of experiment: life span
No of animals: 90 + 90 per dose group

Dose	0	100 ppm	300 ppm	600 ppm
% of animals bearing hepatomas (Male/Female)	4.4 / 0	2.2 / 0	8.9 / 0	14.4 / 1.1

Source: Maltoni *et al* 1986, table 47, p. 73

TCE purity: Epichlorohydrin-free
Strain and species: $B6C3F_1$ mice
Route of exposure: Inhalation
Duration of exposure: 7 hours, 5 days per week for 78 weeks
Duration of experiment: life span
No of animals: 90 + 90 per dose group

Dose (ppm)	0	100	300	600
% of animals bearing hepatomas (Male/Female)	1.1 / 3.3	1.1 / 4.4	3.3 / 4.4	6.7 / 10.0

Source: Maltoni *et al* 1986, table 50, p. 76

e. NTP 1990

TCE purity: Epichlorohydrin-free
Strain and species: B6C3F_1 mice
Route of exposure: oral gavage
Vehicle: corn oil
Duration of exposure: 5 times per week for 103 weeks
Duration of experiment: 103-107 weeks
No of animals: 50 + 50 per dose group

	Male		Female	
Dose (mg/kg)	0	1000	0	1000
Incidence (hepatocellular carcinoma)	8/48	31/50 ($p<0.001$)	2/48	13/49 ($p<0.05$)

TABLE 3 (a-c). *Summary of primary data – kidney carcinogenicity (rats)*

a. NTP 1988

TCE purity: Epichlorohydrin-free
Strain and species: ACI, August, Marshall, and Osborne-Mendel rats
Route of exposure: oral gavage
Vehicle: corn oil
Duration of exposure: 5 times per week for 103 weeks
Duration of experiment: 104 weeks
No of animals: 50 + 50 per dose group

		Male			Female		
	Dose (mg/kg)	0	500	1000	0	500	1000
Incidence (renal tubular adenoma or adenocarcinoma)	ACI	0/50	1/49	0/49	0/48	3/47	1/43
	August	0/50	2/50	1/49	1/49	4/48	0/50
	Marshall	0/49	1/50	1/47	1/50	2/48	1/44
	Osborne-Mendel	0/50	6/50 (p=0.007)	2/50 (p=0.158)	0/50	0/50	1/49

b. NTP 1990

TCE purity: Epichlorohydrin-free
Strain and species: F344N rats
Route of exposure: oral gavage
Vehicle: corn oil
Duration of exposure: 5 times per week for 103 weeks
Duration of experiment: 103-107 weeks
No of animals: 50 + 50 per dose group

	Male			Female		
Dose (mg/kg)	0	500	1000	0	500	1000
Incidence (renal tubular cell adenocarcinoma)	0 / 33	0 / 20	3 / 16 (p<0.05)	0	0	1 / ?

c. Maltoni *et al* 1986

TCE purity: Epichlorohydrin-free
Strain and species: Sprague-Dawley rats
Route of exposure: inhalation
Duration of exposure: 7 hours, 5 days per week for 104 weeks
Duration of experiment: life span
No of animals: 90 + 90 per dose group

Dose (ppm)	0	100	300	600
% of animals bearing kidney adenocarcinomas (Male/Female)	0 / 0	0 / 0	0 / 0	3.1 / 0.7

Source: Maltoni *et al* 1986, table 45, p. 72.

TABLE 4. *Summary of the results of a subsample of epidemiological data.*

Reference	**Exposure**	**Carcinogenic effect**	
		Renal	***Liver***
Spirtas *et al* 1991	TCE, magnitude unknown[a]	Neg.	Pos. for liver and biliary tract[b]
Axelson *et al* 1994	TCE, low to very low[c]	Neg.	Neg.
Anttila *et al* 1995	TCE, low to very low[d]	Neg.	Pos.[e]
Henschler *et al* 1995	Mainly TCE, moderate to very high[f]	Pos.[g]	Not analyzed
Vamvakas *et al* 1998	TCE, moderate to very high[h]	Pos.[i]	Not analyzed
Brauch *et al* 1999	TCE, moderate to high	Pos.[j]	Not analyzed

a = >1 y employment. "Analyses by type of exposure to TCE (frequent vs. infrequent peak exposures, and continuous vs. intermittent low level) did not show any significant patterns" (Spirtas *et al* 1991, p. 519).
b = In white men dying after 1980 (SMR 358, 95% CI 116-836).
c = Mean urinary TCA were <50 mg/L for 81% of the cases (corresponding to an average exposure level of 20 ppm or 110 mg/m^3).
d = Median urinary TCA were 48 µmol/L (6,3mg/L) for men, and 63 µmol/L (8,3mg/L) for women.
e = SIR 6,07, 95% CI: 1,25-17,7 (both gender, more than 20 years since first exposure measurement, mainly TCE exposure).
f = Extreme peak exposure occurred at least every other week.
g = SIR 7,97, 95% CI: 2,59-18,59.
h = For "most subjects".
i = OR 10,80, 95% CI: 3,36-34,75.
j = A statistically significant association between TCE exposure level, incidence of renal cell carcinoma, and the number of somatic mutations in the VHL tumor suppressor gene.
Molecular weight of TCE = 131,5 g/mole (OECD/EU 1996).

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6.1 RISK ASSESSMENT DOCUMENTS

(Abbreviations used in this thesis are given in square brackets.)

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