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Traditional Risk Assessment (RA) and Life Cycle Assessment (LCA): Comparing Two Methodologies

Faria Azad

Supervisors: **Dr. Hanna Gustafsson**, Director Product Stewardship, Perstorp AB

Karen Mackay, Product Stewardship Specialist in Toxicology, Perstorp AB

Xiaomiao Xiong, Product Stewardship Specialist in Toxicology Perstorp AB

Dr. Anna Beronius, Associate Professor, IMM, Karolinska Institutet

Abstract

Industries are required to conduct traditional RA in accordance with REACH regulations, whereas LCA is used by industries to make important decisions on products/process alternatives. As LCA covers the whole life cycle of a product starting from the collection of the raw materials until waste disposal, it has the potential to contribute more in reducing chemical footprint and thus maintaining environmental sustainability. Traditional RA tools used by ECHA such as CHESAR and IUCLID were compared to PEF, the LCA tool recommended by the EU commission, specifically focusing on "Hazard Assessment." The reproducibility of PEF results was also checked by calculating EF and CF following JRC TGD for substances "X" and "Y". The biggest difference between these two methods lies in their aim and scope. While traditional RA aims at establishing safe levels of chemicals for human and environmental health protection, LCA aims at helping industries to choose more environmentally-friendly products to ensure environmental sustainability. In the attempt to calculate EF and CF for LCA, significant differences were observed in some cases between the results produced by JRC and those produced in the current project for both substances. To find out the reason behind the differences, input data in both cases were investigated and discrepancies were found mainly in the human toxicity data input. Therefore, it was evident that the selection of appropriate input data is crucial to LCA. In conclusion, LCA might not be able to replace RA, but it could be used as a complementary tool to support decision-making.

Popular Science Summary

We live in an era where we are reliant on chemicals for inevitable purposes, but are they safe for human health? It is a question that continues to linger. Therefore, it is important to establish a safe level for all the chemicals out there. The mandatory traditional risk assessment performed by industries following REACH regulations by ECHA serves the purpose. But there are more aspects to be considered, such as environmental sustainability, ecosystem health and chemical footprint. It has also been taken into serious consideration to substitute hazardous chemicals with the less hazardous ones whenever possible. With the characteristic of considering the whole life cycle of a product, Life Cycle Assessment has the potential to serve these additional purposes. However, the experts engaged in these two risk assessment methods possess distinct areas of expertise, making it challenging at times for them to comprehend each other's perspectives. This project has attempted to find out the similarities and differences between these two methods to make it easier for these two groups of experts to understand each other. Another purpose of this project was to scrutinize LCA as a risk assessment method. However, it was finally concluded that LCA cannot be used to establish safe levels for chemicals, rather it could help us choose greener products. In addition, LCA needs to be more user-friendly and careful consideration is needed for the selection of input data as this can cause significant changes in the LCA result which will subsequently influence the decision-making.

List of Abbreviations

ADME	Absorption, Distribution, Metabolism and Elimination
AF	Assessment Factor
AOP	Adverse Outcome Pathways
BAF/BCF/BMF	Bioaccumulation Factor/ Bioconcentration Factor/ Biomagnification Factor
CAS	Chemical Abstracts Service
CF	Characterization Factor
CPDB	Carcinogenic Potency Database
CnF	Conversion Factor
CLP	Classification, Labelling and Packaging
CSA	Chemical Safety Assessment
CSR	Chemical Safety Report
CHESAR	Chemical Safety Assessment and Reporting Tools
CTUh	Comparative Toxic Units
DALY	Disability Adjusted Life Years
DNEL	Derived-No Effect Level
ECETOC TRA	European Centre for Ecotoxicology and Toxicology of Chemicals Targeted Risk Assessment
ECHA	European Chemicals Agency
ED10/ ED50	Effective Dose 10/ Effective Dose 50
EF	Effect Factor
ES	Exposure Scenario
EU	European Union
EUSES	European Union System for the Evaluation of Substances
FF	Fate Fraction
GHS	Globally Harmonized System
HTP	Human Toxicity Potential
iF	Population Intake Fraction
IRIS	Integrated Risk Assessment System
IS	Impact Score
ISO	International Organization for Standardization
IUCLID	International Uniform ChemicaL Information Database
JRC	Joint Research Center
JRC TGD	Joint Research Center Technical Guidance Documents
$Kdeg_A$	Degradation Rate in Air
$kdeg_{Sd}$	Degradation Rate in Sediment
$kdeg_{Sl}$	Degradation Rate in Soil
$Kdeg_W$	Degradation Rate in Water
Kow	n-Octanol water partition coefficient
LCA	Life Cycle Assessment
LCI	Life Cycle Inventory
LCIA	Life Cycle Impact Assessment
LOAEL	Lowest Observed Adverse Effect Level
LOEL	Lowest Observed Effect Level
MoA	Mechanism of Action
NOAEL/NOAEC	No-Observed Adverse Effect Level/ No-Observed Adverse Effect Concentration
NOEL	No-Observed Effect Level
PBT	Persistent, Bioaccumulative and Toxic
PEF	Product Environmental Footprint
pKa	Dissociation constant
PNEC	Predicted No-Effect Concentration
RA	Risk Assessment
RCR	Risk Characterization Ratio
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
SDG	Sustainable Development Goals
SDS	Safety Data Sheet
SSbD	Safe and Sustainable by Design
XF	Exposure Factor

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1. Introduction

1.1 Background and Relevance of the Project

Although chemical use has become inevitable for humans in everyday life, there is also scientific evidence to suggest that chemicals can pose a great threat to human health if not used and managed properly (1). This is why risk assessment of chemicals for both human health and the environment is required for regulatory compliance in most cases. All the manufactured/imported chemicals within the European Union (EU) should be registered at ECHA (European Chemicals Agency) according to the European Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) Regulation EU 1907/2006 (2).

The European REACH ((EU) No 1907/2006) regulation came into force on 1 June 2007 intending to maximize the protection of both human health and the environment against the risk posed by chemical exposure, without compromising the productivity of the chemicals industry across the EU (2). Sufficient information on the intrinsic properties of the substance, uses as well as tonnages related to each use and condition, are crucial for risk assessment (2, 3). However, toxicity data is not required if the substance imported or manufactured is less than 1 ton per annum (3). Regulatory toxicity data requirements are termed "Information Requirements of chemicals" under REACH. The information requirements increase as the tonnage increases. Moreover, industries are tasked with assessing hazards with regard to the intrinsic properties of the substances as well as available toxicity data and also evaluating potential risks associated with these substances (2).

Industries must not only acquire and evaluate all existing data on the substance but also ensure updates to the database. For example:

- changes in the annual or total quantities manufactured or imported, if these result in a change of tonnage band,
- any change in the classification and labelling of the substance,
- or, any new uses that may affect human and environmental exposure.

Additionally, they are obliged to incorporate any newly available data on toxicological and ecotoxicological effects, particularly if such information could influence the assessment of the substance's potential risk. (3- REACH regulation- Article 22). In addition to the REACH regulation, the chemical industries also must comply with the Classification, Labelling and Packaging (CLP) regulation ((EC) No 1272/2008), which aligns the EU system of

classification, labelling and packaging of chemical substances and mixtures to the Globally Harmonised System (GHS) (4).

1.2. Traditional Risk Assessment Tools

The traditional human health risk assessment method usually follows the steps outlined in Figure 1.

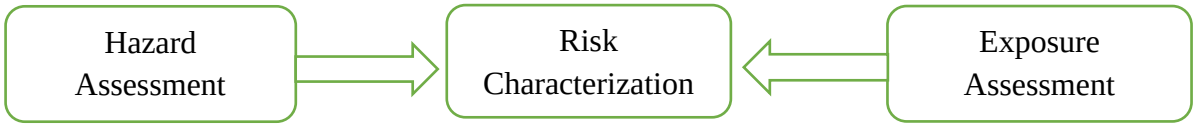

Figure 1. Steps of traditional human health risk assessment method [Adopted from REACH (5)]

As seen from the figure mentioned above, to make informed regulatory decisions through a scientific rationale, Hazard Assessment, Exposure Assessment and Risk Characterization are performed under REACH/CLP regulation (6). This involves estimating the probability of the occurrence of adverse health effects on humans and the environment for specific exposure to a substance and describing the uncertainty and variability of the estimates as well. Thus, traditional quantitative Risk Characterization is usually evaluated by calculating Risk Characterization Ratio (RCR). RCR is derived by comparing exposure levels (exposure assessment) with no-effect-levels (hazard assessment) where exposure could be calculated considering either a "realistic worst-case scenario" or an "average exposure scenario". Risk is assumed to be unacceptable if the RCR exceeds the value of 1 and acceptable if the value is below 1 (7).

As per Annex VII of the REACH Regulation, companies are responsible for the Chemical Safety Assessment (CSA) of substances, which they manufacture or import in quantities exceeding 1 ton per year. These data are then conveyed to the European Chemicals Agency (ECHA) (2) through a registration dossier, which includes hazard information and, if applicable, an assessment of the substance's risks and proposed risk management measures.

1.2.1. IUCLID

IUCLID (International Uniform ChemicaL Information Database) is a software application system developed by the European Commission which plays a central role within the IT frameworks of organizations facilitating the management of vast amounts of scientific data concerning chemicals within regulatory frameworks, such as the CLP and REACH regulations in the EU (8, 9).

"One substance, one registration" is the principle of REACH registration process requiring manufacturers and importers of the same substance to submit data jointly (2, 3). Nevertheless, all the companies also have their own registration dossier. That is why the information provided needs to be consistent and sufficient to confirm the identity of the substance. (8). Each dataset within IUCLID is distinguished by the substance identity number (inventory number or CAS number), name of the legal entity, and the creation date. (8). In addition, there is provision of a lead registration dossier submitted by the lead registrant and is considered as the lead dossier to be used for that substance. (2, 3).

To comply with the REACH regulation, there are around 11 sections on IUCLID with several subsections which need to be filled out by the registrants. (10, 3- REACH Regulation- Article 11). The sections are shown in Table 1 below.

Table 1. Information Requirements and responsible entities on REACH (10, 3- REACH Regulation- Article 11)

No.	Sections	Responsible entity
1	General Information	Information is submitted by each registrant on their own dossier
2	Manufacture, Uses & Exposure	
3	Classification & Labelling	Submitted mainly by the lead registrant, could also be submitted by each registrant separately if needed
4	Physical and Chemical Properties	
5	Environmental Fate and Pathways	
6	Ecotoxicological Information	
7	Toxicological Information	
8	Analytical Methods	
9	PBT Assessment	Could be submitted by either the lead registrant or separately by each registrant depending on the agreement
10	Guidance on Safe Use	
11	Assessment Reports	

1.2.2. CHESAR

CHESAR stands for Chemical Safety Assessment and Reporting Tool. ECHA has created this tool to assist companies in conducting their CSA. It also helps companies prepare their chemical safety reports (CSRs) and formulate exposure scenarios (ESs) to enhance communication throughout the supply chain (11). A CSR is required as a part of a registration dossier if the tonnage of production/import is 10 tonnes or more per year (3-REACH Regulation, Article 14).

According to Annex I of REACH, the hazard assessment data for the substance must be available for the risk assessment on CHESAR to begin. CHESAR imports all the substance properties needed for exposure assessment and risk characterisation from the IUCLID registration dossier and thus ensures consistency between the dossier and the Chemical Safety Assessment (CSA) (11). Subsequently, it is also possible to transfer the data on use description and exposure assessment to the registrant's IUCLID database.

Besides the regulatory demand, the importance of risk assessment and sound management of chemicals is increasing focus, also due to several international agreements in place as well as European and global goals towards sustainable development. (12, 13). To keep up with this rapidly changing world, transitioning to less hazardous chemicals, whenever possible, throughout the entire supply chain, is of utmost importance (12). Therefore, it is not a surprise that responsible management of chemicals and waste, for sustainable development, is also a part of the European Green Deal. The "European Green Deal", proposed in 2019 aiming to reduce climate gas emissions, (14), also proposes "Chemicals strategy for Sustainability" encouraging the development of safe and sustainable alternatives to dangerous chemicals to take a step forward towards a toxic free environment (1).

1.3 Chemical Footprint

The concept of footprint is to be able to measure and describe the impact of human activities on the environment and thus global sustainability (15, 16). Following this idea of footprint, chemical footprint could simply be defined as an indicator of the impact of chemicals on environmental sustainability. The chemical impact on environmental sustainability could be illustrated as ecotoxicity, climate change, ozone depletion, global warming etc. However, from the life cycle-based approach, chemical footprint is identified as a combination of the chemical hazard and potential of exposure from both the ingredients and the final product during its life cycle. Thus, assessing chemical footprint requires the quantification of the potential impacts not only from the chemicals used/ produced or modified during the life cycle of the product, but also other related emissions, e.g. from auxiliary chemicals and emissions from combustion (15).

1.4 Life Cycle Assessment (LCA)

Life Cycle Assessment (LCA) is a comprehensive method to assess the potential environmental and human health impact of a product, process or service from cradle to grave perspective (7). It is a framework that sums up all the chemical emissions and activities of the product starting from resource extraction, through production of materials and manufacture and consumption of products, until waste management after use as well as processing, meaning the entire life cycle of a product is assessed (17).

In short, LCA addresses the relative risk for human toxicity and ecotoxicity indicators within or between the life cycle of the products or services. Thus, the aggregated measure of both indicators performed in an LCA is identified as chemical footprint.

1.5 LCA Based Risk Assessment Tools

There are four main phases within an LCA:

1) Goal and scope definition: In this step, the assessor identifies the purpose of the study which determines the time and resources needed to obtain the most relevant result for the decision-making process. An appropriate "Functional unit" is selected carefully as a basis of comparison between two or more products. An example of such functional unit could be "a battery sized to provide 5,000 milliamp hours of capacity over a minimum service life of four years of daily use". Selection of impact categories, impact category indicators and characterization models are crucial at this stage (7). All relevant impact categories should be covered in an LCA as per ISO 14044:2006 (18).

2) Inventory analysis (LCI): All relevant data on environmental inputs (resources) and environmental outputs (emissions and waste) associated with a product or process throughout its entire life cycle are collected and compiled. This includes energy and raw material requirements, atmospheric emissions, waterborne emissions, solid wastes, and other releases. Thus, an inventory analysis provides a comprehensive list of pollutants released into the environment and the consumption of energy and materials. This data can be categorized based on life cycle stages or other relevant categories as well (7).

3) Life-cycle impact assessment (LCIA): In this step, the contribution of these inputs and outputs are assessed in relation to a broad range of human health and environmental impacts (7). This step involves assigning the results from LCI to impact categories, modelling LCI impacts with science-based conversion factors named "Characterization factors" (CFs), and expressing potential impacts in comparable ways. As an example, product "A" has global warming potential of 200-ton CO2 equivalent whereas product "B" has a global warming potential of 450-ton CO2 equivalent.

In LCIA (life cycle impact assessment), the impact of a substance (on human health or environment) emitted in an environmental compartment (air, water, soil) is estimated by multiplying the mass of substance emitted during the process with the CF of that particular substance. The final result achieved through an LCIA assessment, is called the Impact score (IS). LCIA helps understand and evaluate the relative differences in potential environmental impacts [e.g. global warming potential, human toxicity potential (HTP) etc.] for each product to be compared.

The impact categories in LCA represent the categories/classes of human health and environmental issues of concern (19). Common impact categories used are natural resource use, climate change, ozone depletion, acidification, photochemical ozone formation, eutrophication, HTP (cancer and non-cancer) (7). HTP refers to the impact of toxic substances being emitted to the environment on humans.

The results from LCI analysis need to be converted to the common unit of the impact category indicator (19). The impact categories are then quantified through indicators which could either be calculated as midpoint or endpoint. Midpoint impact indicators are a point before the endpoint in the cause-effect chain of that specific impact category (20). The unit for midpoint indicator for human toxicity impacts/potential is Comparative Toxic Units (CTUh) and Disability Adjusted Life Years (DALY) for endpoint category (19).

4) Life-cycle interpretation: This is the last step which helps us evaluate the findings of either LCI or LCIA, or both in relation to the defined goal and scope to reach conclusions (21).

The LCA framework incorporates the phases and is also internationally standardized (ISO 14044, 2006) (18). The methodological framework is shown in figure 2 below.

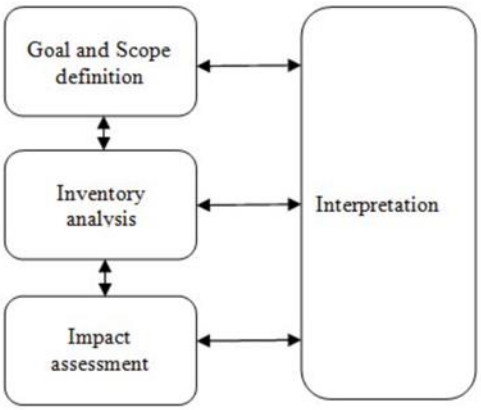

Figure 2. Common methodological framework for LCA according to ISO 14040. (Obtained and modified from 21, 22, 23, 24, 25)

1.5.1 Characterization Factor (CF)

A specific characterization model is chosen according to the goal and scope defined by the user to derive the Characterization Factors (CF) (19). For human toxicity related impact categories, the CF is a quantitative representation of the potential toxicological impact of a specific chemical emission on human health (26). CFs could be calculated both with midpoint

indicators and endpoint indicators. The midpoint CFs for human toxicity indicate the increase in morbidity or disease cases in the total human population per unit mass of a chemical emitted to a given environmental compartment while the endpoint CFs represent the increase in damage or disability. For example, LCIA model named "USEtox" includes a multimedia fate model that calculates fate and exposure given emissions to certain emission compartments. In this

model, environmental compartments or emission compartments are air, water, and soil from different sources in either continental or global scale. The unit of midpoint and endpoint CFs for human toxicity is CTUh/kg emitted or disease cased/kg emitted, and DALY/kg emitted, respectively (27, 28).

CF can be calculated from the following equations:

$$CF = iF * EF \text{ [Equation-1]}$$

$$iF = FF * XF \text{ [Equation-2]}$$

Where EF= Effect Factor, iF= Population intake fraction, XF= Exposure Factor (XF) and FF= Fate Factor (26,27). FF and XF express the change in dissolved concentration of a chemical in an environmental compartment caused by a change in the emission (27).

1.5.2 Effect Factor (EF)

The human toxicological effect factor (EF) describes the estimated increase in lifetime disease probability (expressed as no. of cancer/non-cancer disease cases) due to increase in lifetime intake of a chemical/substance by human population. It is expressed through the unit of cases/kg intake. EF is needed to derive CF from Equation 1.

Both RA and LCA provide a clearly structured framework with well-defined methodological steps but have different risk assessment techniques (7). While the traditional RA method can assess risk of chemicals/ substances, could be either site-specific (only contains relevant hazard information for the specific site) or site-generic (not adapted to a specific site, gives an overall view of the risk assessment) and concentrate on human and environmental health; LCA methods are usually site-generic and cover a far broader range of environmental impacts comparing specific products/ services (7). From this point of view, it seems worth considering if these methods can complement each other in terms of human health risk assessment.

1.6 The Aim of the Thesis Project

The aim of this project is to compare the similarities and the differences between traditional RA and LCA methodology with respect to human health risk assessment. The comparisons between these two methods will be established through case studies of two plasticizers, one of them is phthalate (Substance "X") and the other one is non-phthalate (Substance "Y").

This project specifically aims to:

1. Give an overview of the comparison between traditional RA and LCA as risk assessment methods.
2. Compare the physicochemical and fate properties input data/parameter used in both methods.
3. Compare the Assessment factors (AF) used in RA and Conversion factors (CnF) in LCA to extrapolate human toxicity data from *in vivo* experimental data.
4. Calculate Toxicological Human Health EF and Midpoint Human Health CF for LCA for substances "X" and "Y".

In addition, scrutinizing the trustworthiness and reproducibility of LCIA calculations in relation to traditional RA is also considered to be within the scope of this project.

2. Methods and Materials

2.1 Traditional Risk Assessment Tool

2.1.1 IUCLID

IUCLID is the tool where substance data are gathered by the registrants. The substances "X" and "Y" have already been in production for years, so the data were already available for both.

The substances "X" and "Y" are not under any hazard classification, and so were not under the obligation to go through the CSA. However, to achieve "Aim 2", the data related to the substances of interest were imported directly from the registrant dossier on the IUCLID database to CHESAR, as would be done in a CSA.

2.1.2 CHESAR

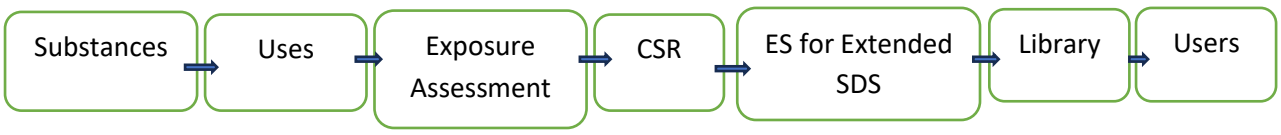

Figure 3. Functional workflow on CHESAR

As portrayed in figure 3 above, CHESAR is divided into 7 major groups of functionalities which are called "Boxes". Box 1 is named as "Substances". This step involves importing substance properties directly into CHESAR and determining the scopes for exposure assessment (route/types of effects for humans, and environmental compartments to be covered) as well as the type of risk characterization (quantitative/qualitative) needed.

Box 2 is named as "Uses" where it is crucial to describe the relevant uses of the substance following the life cycle tree structure (description of all life cycle stages) so that the use descriptions and the exposure assessment align with each other as the exposure assessment will be based on the use descriptions. The tonnage breakdown for different uses can be inserted in the life cycle tree. Additionally, both human health and environmental aspects are considered, and contributing activities can be created for each use. The life cycle for a risk assessment on CHESAR usually starts from the manufacture of a specific substance/chemical in a site and goes all the way through the end uses/service life of the articles when it is being used by consumers/industrial workers/professionals.

Depending on the information provided in Box 1 and Box 2, Box 3 is used to report the conditions for safe use for each contributing scenario and calculate the exposure estimate. CHESAR is designed to compare the exposure estimates to the DNEL/PNEC level and thus concludes if and how safe use of that substance can be made possible. Tools such as ECETOC TRA (Targeted Risk Assessment) are used to assess the health risks of exposure to chemicals for workers and consumers (29). EUSES fate model is used for the environmental exposure estimates (30) which can be customized to change default release factors (31). The last step for quantitative risk assessment is to calculate the RCR for different exposure scenarios and generate CSR. Box 4 is where the CSR is generated.

After importing the data from IUCLID to CHESAR, steps starting from Box 1 up to Box 3 were followed as per CHESAR user manual for the calculation of the RCR which is needed for better understanding of "Aim 1" for my research project. Derived No-Effect Level (DNEL) values were already calculated on the IUCLID following the below equation:

$$DNEL = \frac{NOAEL/NOAEC}{Assessment\ Factors\ (AF)}$$ [Equation- 3]

The AFs are used to reduce the uncertainty of the calculated DNEL which were also compared to CnFs from LCA to achieve "Aim 3".

2.2 LCA based tools

For Goal and Scope Definition for the relevant steps to perform LCIA, the impact category chosen was Human Toxicity Potential (cancer and non-cancer) with a midpoint indicator of Comparative Toxic Unit for Human Health (CTUh).

2.2.1 Product Environmental Footprint method (PEF)

LCA has different tools and models to calculate LCIA, therefore, seemed reasonable to select one tool to compare with the RA. The tool chosen was Product Environmental Footprint (PEF) as it has been recommended by the European Commission as a standard impact assessment method (32). PEF was introduced with the purpose of reducing the environmental impact of products throughout the supply chain by making the comparison of environmental footprint measurement of the products more feasible and equal (32, 33). It is a methodological framework providing specific guidelines to perform an LCA.

PEF uses the USEtox multimedia fate model, which combines chemical fate and exposure with toxicological data (33, 34) and calculates the CFs for human toxicity estimating substance distribution in following compartments: indoor (household indoor air, industrial indoor air), urban (urban air), continental (rural air, freshwater, sea water, agricultural soil and natural soil) for 2 routes (ingestion and inhalation) of exposure (27, 28). In addition, the USEtox model is considered the most reliable model to address the midpoint indicators of substances for aquatic freshwater ecotoxicity and human toxicity (33, 35). Thus, USEtox accounts for 4 human EFs: cancer from ingestion exposure, non-cancer effects from ingestion exposure, cancer from inhalation exposure, and non-cancer effects from inhalation exposure (36).

The data input parameters for LCIA were checked through using the USEtox model following the European Joint Research Center Technical Guidance Documents (JRC TGD) and then compared with the data requirements on CHESAR. In addition, this project has focused only on the third step of the LCA by calculating Toxicological Human Health EFs and Midpoint Human Health CFs for substances "X" and "Y" following the JRC TGD.

2.2.2 Calculation of ED50 and Toxicological Human Health EF

Calculating the EF was one of the several aims of this project. However, it is crucial to calculate ED50 values of the substances of interest to calculate the EF value. ED50 means the lifetime daily dose of a substance at which 50% of the population is affected. As required by the USEtox

model, both ED50noncancer and cancer values for oral and inhalation routes are to be calculated. Though EF is automatically calculated when ED50 values are put in the USEtox model, it can also be calculated manually following a simple equation (Equation 8) assuming linear dose-response curves for each disease endpoint and exposure route (37).

The first step is to calculate ED50chronic value for oral and inhalation route of exposure.

$$ED50, chronic, oral\ \left[\frac{mg}{kg\ day}\right] = \frac{REACH\ value\left[\frac{\frac{mg}{kg\ bw}}{day}\right] * CnFreferencepoint}{CnFendpoint} \text{ [Equation- 4]}$$

$$ED50, chronic, inhalation\ \left[\frac{mg}{m3}\right] = \frac{REACH\ value\left[\frac{mg}{m3}\right] * CnFreferencepoint}{CnFendpoint} \text{ [Equation- 5]}$$

$CnF_{referencepoint}$ means the Conversion factors from the related dose descriptors, which follow this order of priority: NOAEL, NOEL, LOAEL, and LOEL. The $CnF_{endpoint}$ refers to the Conversion factors from the endpoint of the toxicological studies, which follow this order of priority: chronic->sub chronic or semi chronic->subacute. However, for substance "X", the lowest NOAEL on REACH-IUCLID database was not of human relevance, so a human relevant NOAEL was chosen instead. For substance "Y", there was only one NOAEL value to be selected.

For both substances X and Y, there are NOAELs from studies conducted in the context of REACH and the toxicological endpoints are, repeated oral dose sub chronic toxicity study, and subacute inhalation toxicity study. According to the JRC TGD, the $CnF_{referencepoint}$=9 if we have a NOAEL, $CnF_{endpoint}$=2 for conversion to chronic from sub chronic study. And $CnF_{endpoint}$=5 for conversion to chronic from sub-acute study. Later, we compared the CnFs from LCA with the AFs used by ECHA REACH guidance in IUCLID which is explained in the "Results" section.

The next stage is to calculate the ED50 value for lifetime following the equations below:

$$ED50ingestion\left[\frac{\frac{kg}{person}}{lifetime}\right] = \frac{ED50chronic,oral\left[\frac{mg}{kg\ day}\right] * bodyweight[kg] * lifetime[year] * 365[\frac{day}{year}]}{CnFspecies * 10^6[\frac{mg}{kg}]} \text{ [Equation- 6]}$$

$$ED50inhalation\left[\frac{\frac{kg}{person}}{lifetime}\right] = \frac{ED50chronic,inhalation\left[\frac{mg}{m3}\right] * inhalation\ rate\left[\frac{m3}{day}\right] * lifetime[year] * 365\ [\frac{day}{year}]}{10^6[\frac{mg}{kg}]}$$ [Equation- 7]

This is calculated assuming that the average bodyweight of a person is 70kg, an average lifespan is 70 years, and the average inhalation rate is 13m^3/day. The extrapolation factor for interspecies difference ($CnF_{species}$) has been considered 4.1 for ingestion as it was an *in vivo* study on rats. There is no extrapolation factor for the inhalation study.

ED50cancer values could not be derived due to lack of data. Neither of the substances had any relevant data on CPDB (Carcinogenic Potency Database) or IRIS (Integrated Risk Information System). In addition, both substances are considered as non-mutagenic as per experimental studies in IUCLID database. So, the total ED50 value ideally covering both cancer and non-cancer, is equal to the ED50 value for non-cancer for these substances.

The last step is to calculate EF by the following equation:

$$EF = \frac{0.5}{ED50}$$ [Equation-8]

2.2.3 Calculation of Midpoint CF for Human Toxicity

To achieve "Aim 4", USEtox version 2.13 was used to calculate the CFs for the substances "X" and "Y". Data on physicochemical properties, data on environmental fate and pathways as well as the ED50 value for ingestion and inhalation derived through following the equations No. 4-7 were used as input data on the "Substance data" worksheet on USEtox. "Default USEtox" values were selected for regional landscape and indoor data as recommended by the manual. The final step was to run the series of the substances and read the results.

In addition, to assess the reproducibility of the LCIA results, we used input data from JRC supplementary materials (extracted from a compressed folder named "Saouter et al, 2018 - SM updated to EF3_1") on USEtox version 2.13 and compared the result with the EF 3.1, result produced by JRC on the excel worksheet named "EF-LCIAMethod_CF(EF-v3.1)" for substance "X". We performed the same comparison for substance "Y" but with input data and results from JRC supplementary materials as EF 3.1 results were not available for that substance.

As a matter of fact, USEtox could derive a list of CFs for several emission compartments which does not match all the emissions compartments for PEF method. Therefore, JRC converted CFs for substance "X" from "USEtox emissions compartment" to "EF emissions

compartment", following the equivalence reported in Table 48 of the JRC TGD (page-76). The comparison for substance "X" was done following emission compartments from both USEtox and PEF while only USEtox emission compartments were compared for substance "Y" to keep the comparison in line with the results from JRC supplementary materials.

2.3 Literature Search

Single topic search with "Life cycle assessment", "Traditional Risk Assessment" "CHESAR", "IUCLID" and "Product Environmental Footprint" was made on PubMed at the first attempt which generated 7099, 16880, 2, 10 and 4154 results respectively. Then strings were made with search terms "(Life cycle assessment) OR (Product Environmental Footprint) AND (CHESAR) OR (IUCLID) OR (Traditional Risk Assessment)" producing 99 results. Other search strings such as "(Life cycle assessment) AND (Traditional Risk Assessment), "(Life cycle assessment) AND (CHESAR)", "(Product Environmental Footprint) AND (CHESAR)" produced 86, 14 and 4 results respectively.

2.4 Ethical permits

Ethical permits were not needed for this research project as no *in vitro* or *in vivo* experiment was performed. Additionally, no human data was used for this project.

3. Results

3.1 Overview of the comparison between RA and LCA as risk assessment methods

The overview of the comparison of main components and scope between the two methods are shown in Table 2.

Table 2. Comparison overview between RA and LCA

Category	RA	LCA
Characteristics	Method with detailed analytical guidance	Method with detailed analytical guidance
Uses	Primarily used for the risk assessment of chemicals	Primarily used to compare products or processes
Aim	The aim is to establish safe levels for chemicals	The aim is to assess relative risk of products, does not address safety of the products
Contribution to the supply chain/ Life cycle considered	Begins with the manufacture of the products up to the whole chain of the downstream users	Begins from the production of the raw materials until the waste disposal, covering both upstream and downstream users (cradle-to-grave approach)
Inclusion of transformed substances	If the substance of interest transforms into another substance along the supply chain, risk assessment of the other substance is performed separately	Transformation products are normally not included, the fate and effects of the parent compound are focused

Scope	Covers acute and chronic human health risk assessment from direct and environmental exposure as well as environmental risk assessment.	Covers ecosystem, human health impacts as well as environmentally mediated impacts by indirect exposure.
Final result	Final result is calculating RCR which quantifies and compares the exposure with effect levels which identifies if and how the chemical can be safely used	Final result is calculating the Impact Score which provides the relative risk scores on different impact categories
Type of approach used	RA is a tiered approach involving a hierarchy (tiers) of tests which shows us if the substance is safe for human and environmental health depending on the exposure scenario	LCA is an iterative approach which shows the most significant environmental impacts caused by a product and at which stage(s) in the life cycle these impacts occur the most

3.2 Comparison of data input parameters both for CHESAR and LCA

Substances "X" and "Y" both are organic substances, thus there are 8 mandatory "physicochemical and fate properties" of the substances to be used in USEtox as per JRC TGD. However, default values are used by the model if no specific data point is available for the non-mandatory properties. Different sources were used to collect these data following the JRC-TGD. When experimental data were not available for certain properties on REACH-IUCLID database, EPI Suite software was used according to the same Guidance document. EPI Suite is a QSAR tool that estimates physicochemical and environmental fate properties (38). All the properties of the substances for RA in CHESAR were imported from IUCLID substances database.

The physicochemical properties and environmental fate properties for data input in both USEtox and CHESAR are described in Table 3 and Table 4 respectively.

Table 3. Physicochemical properties data input on CHESAR and PEF

Physicochemical properties for CHESAR	**Data sources for CHESAR**	**Physicochemical properties for PEF**	**Data sources for PEF in USEtox**
Molecular weight#	IUCLID	Molecular weight (MW)*	REACH-IUCLID database
Vapour pressure# (For liquid substances)	IUCLID	Vapour Pressure at 25°C (Pvap25)*	REACH-IUCLID database. MpBpVpWIN model in EPI Suite must be used if experimental data is not available
Partition Coefficient (Log Kow)	IUCLID	n-Octanol water partition coefficient (Kow)*	REACH-IUCLID database, KowWIN model in EPI Suite must be used if data is not available on IUCLID

Henry's Law Constant (in Pa m3/mol)	IUCLID	Henry's Law Constant at 25c (K_H25°C)	REACH-IUCLID database, HenryWIN model in EPI Suite must be used if experimental data is not available
Water solubility	IUCLID	Water solubility (at 25°C)* (Sol25)	REACH-IUCLID database, WATERNET model in EPI Suite must be used if experimental data is not available
Dissociation Constant (pKa)	IUCLID	Acid Dissociation Constant is reported with 3 parameters: pKa chem class pKa.gain pKa.loss	ADMET predictor is used. pKa Chem Class is assigned based on the presence/absence of pKa.loss and pKa.gain. There are 4 classes on the model- acid, base, neutral & amphoter. If no class is selected, the default class will be "neutral" and the pKa.gain and pka.loss will be set to 0 & 14, respectively
-	-	Organic carbon/water partition coefficient(Koc)	REACH-IUCLID database, KocWIN model in EPI Suite must be used if experimental data is not available
Physical state at 20°C and 1013hPa#	IUCLID	-	-
Melting point#			
Boiling point			
Relative density			
Solubility in mg/100g standard fat			
Solubility in organic solvents			
Surface tension (-concentration in mg/L)			
Oxidation reduction potential in mV			
Viscosity			

*means data inputs mandatory for USEtox which must be available to run the model

#means data inputs mandatory for CHESAR which must be available to run the ECETOC TRA workers and consumer model

Table 4. Fate properties data input on CHESAR and PEF

Fate properties for CHESAR	**Data sources for CHESAR**	**Fate properties for PEF**	**Data sources for PEF in USEtox**
Degradation rate constant with OH radicals DT50 for phototransformation in air DT50 for hydrolysis DT50 for phototransformation in water DT50 for phototransformation in soil	IUCLID QSAR results can be used if applicable	Degradation rate in air ($kdeg_A$) for PEF*	AOPWIN3 model in EPI Suite should be used if no experimental data is available. In that case, the default [OH] is set at 1.5E06 molecules (radicals)/cm^3 per 12 hours of daylight which is multiplied with OH concentration in air (Derived from a reliable database e.g. CompTox) and divided by a factor of 2 to reflect degradation during 12 hours per day
Biodegradation in water: screening tests DT50 in freshwater DT50 in marine water	IUCLID- QSAR results can be used if applicable Divided into 4 categories- i. Readily biodegradable ii. Biodegradable, failing 10-days iii. Inherently biodegradable iv. Not readily biodegradable	Degradation rate in water ($kdeg_w$)*	Half-life should be assigned based on the category derived from REACH-IUCLID database and then default values should be used accordingly for calculating degradation rate constant (s-1), otherwise BIOWIN3 model in EPI Suite must be used if data is not available on IUCLID as per USEtox manual
DT50 in freshwater sediment DT50 in marine water sediment	IUCLID Study is not conducted if the substance is readily biodegradable	Degradation rate in sediment ($kdeg_{sd}$)*	As per USEtox manual and as suggested in EPI Suite, division factor 9 is applied to extrapolate $Kdeg_{sd}$ from $Kdeg_w$
DT50 in soil	IUCLID Data could be waived if not necessary (the substance is readily biodegradable) QSAR results can be used if applicable	Degradation rate in soil ($kdeg_{sl}$)*	As per USEtox manual and as suggested in EPI Suite, division factor 2 is applied to extrapolate $Kdeg_{sl}$ from $Kdeg_w$
Bioaccumulation (BMF): in fish Bioaccumulation (BCF): Aquatic species	IUCLID- QSAR results can be used if applicable	Bioaccumulation Factor in fish (BAF_{fish}) BAFmeat	BIOWIN3 model in EPI Suite must be used

Bioaccumulation (BCF): Terrestrial species		BAFmilk	
		BAFleaf	
		BAFroot	

*means data inputs mandatory for USEtox which must be available to run the model

-means Not applicable

3.3 Comparison between AFs from ECHA REACH Guidance and CnFs from JRC TGD

AFs are numerical values used in traditional RA in order to address the uncertainties while extrapolating experimental data to relevant human exposure scenario (39). On the other hand, CnFs are used in PEF to translate measurements or values (33). The comparison between AFs and CnFs used in RA and PEF respectively is shown below in Table 5.

Table 5. Comparison between AFs and CnFs

Factors		**AFs**		**CnFs**	
Dose-response relationship		LOAEL to NOAEL	3-minimum/default/ in majority of cases, 10-maximum/in exceptional cases	LOAEL to ED_{50}	2.5
		Other issues	1	NOAEL to ED_{50}	9
Duration of exposure		Subacute to chronic	6	Subacute to chronic	5
		Subchronic to chronic	2	Subchronic to chronic	2
		Subacute to subchronic	3	-	-
		Chronic to lifetime	1	Chronic to chronic	1
Interspecies differences	Differences in metabolic rate	4* (Allometric scaling factor for rats)		4.1# (Allometric scaling factor for rats)	
	Toxicodynamic differences	2.5 1 or 2.5 (For local effects)		-	
Intraspecies differences	Workers	5		-	
	General population	10		-	
Quality of database		Case by case (≥1) Good quality data= 1		-	

- = Not applicable
* = Only applicable for oral and dermal route
\# = Only applicable for oral route

3.4 Calculation of Human Toxicological EF and Midpoint Human Health CF

3.4.1 Calculation of Human Toxicological EF

The calculation was performed using equations 4-8. As described earlier, the human relevant NOAELs and NOAECs were selected from the REACH-IUCLID database. Then, the appropriate conversion factors were applied to the equations. The result of the calculation of ED50 and EF for both substances are presented in the Tables 6-7 below.

Table 6. ED_{50} values for Substances "X" and "Y"

ED_{50} categories	**Substance "X"**	**Substance "Y"**
$ED50_{chronic, oral}$ [Equation-4]	882 mg/kg/day	4500 mg/kg/day
$ED50_{ingestion}$ of a person for lifetime [Equation-6]	384.74 kg/person/lifetime	1962.99 kg/person/lifetime
$ED50_{chronic, inhalation}$ [Equation-5]	90 mg/m^3	2250 mg/m3
$ED50_{inhalation}$ of a person for lifetime [Equation-7]	29.89 kg/person/lifetime	4024.12 kg/person/lifetime

EF was also calculated using Equation 8 which can also be auto calculated on the USEtox model when all the ED50 values are provided as an input.

Table 7. EF values for substances "X" and "Y"

EF categories	**Substance "X" (disease cases/kg intake)**	**Substance "Y" (disease cases/kg intake)**
EF for ingestion	0.001	0.00025
EF for inhalation	0.016	0.0001

3.4.2 Calculation of Midpoint CFs for human toxicity

The following CFs presented in Table 8 were obtained through data input on the USEtox model following the JRC TGD on PEF:

Table 8. Midpoint CFs for human toxicity (total) for substances "X" and "Y"

Emission compartments	**Substance "X" (CTUh/kg emitted)**	**Substance "Y" (CTUh/kg emitted)**
Household Indoor air	7.14E-05	5.84E-07
Industrial indoor air	2.63E-06	7.18E-08
Urban air	7.06E-07	5.67E-08
Continental Rural air	3.51E-07	5.82E-08
Continental Fresh water	2.81E-09	9.73E-09
Continental Sea water	5.16E-11	6.30E-10
Continental Natural soil	1.37E-12	5.57E-13
Continental Agricultural soil	5.10E-10	2.19E-10

In addition, as discussed earlier, we compared the CFs already calculated and published by JRC, CFs obtained using input data from JRC Supplementary materials and CFs obtained by data input following the JRC TGD. The comparison is presented in Tables 9 and 10.

Table 9. Comparison between results for midpoint CFs for human toxicity (total) for substance "X"

Emission compartments		**Result from EF 3.0 (CTUh/kg emitted)**	**Putting JRC supplementary material input data on USEtox 2.13 (CTUh/kg emitted)**	**Putting my input data following JRC TGD on USEtox 2.13 (CTUh/kg emitted**
USEtox	**PEF**			
Household Indoor air	-	-	7.34E-05	7.14E-05
Industrial indoor air	-	-	4.55E-06	2.63E-06
-	Emission to air indoor- Average of household/industrial indoor air	3.9152E-05	3.89E-05	3.7E-05
Urban air	Emission to urban air close to ground	2.7941E-06	2.61E-06	7.06E-07
Continental Rural air	Emissions to non-urban air or from high stacks, Emissions to lower stratosphere and upper troposphere	2.5287E-06	2.39E-06	3.51E-07
-	Emissions to air, unspecified- Average of urban/ continental rural air	2.6614E-06	2.66E-06	5.28E-07
Continental Fresh water	Emissions to Fresh water	1.68E-07	1.82E-07	2.81E-09
Continental Sea water	Emissions to Sea water	1.41E-08	1.56E-08	5.16E-11
-	Emissions to water (unspecified)- Average of fresh water and sea water	1.0167E-07	9.88E-08	1.43E-09
Continental Natural soil	Emissions to Natural soil	2.1439E-09	2.03E-09	1.37E-12
Continental Agricultural soil	Emissions to Agricultural soil	7.478E-09	7.37E-09	5.10E-10
-	Emissions to soil (unspecified)- Average of natural soil and agricultural soil	4.8109E-09	6.14E-09	2.55E-10

- = Not applicable

Table 10. Comparison between results for midpoint CFs for human toxicity (total) for substance "Y"

Emission compartments	Result from JRC supplementary materials	Putting JRC supplementary material input data on USEtox 2.13	Putting my input data following JRC TGD on USEtox 2.13
Household Indoor air	4.35E-05	4.34E-05	5.84E-07
Industrial indoor air	1.54E-06	1.51E-06	7.18E-08
Urban air	3.68E-07	3.42E-07	5.67E-08
Continental Rural air	1.56E-07	1.33E-07	5.82E-08
Continental Fresh water	1.06E-08	1.05E-08	9.73E-09
Continental Sea water	1.12E-10	1.00E-10	6.30E-10
Continental Natural soil	7.27E-12	6.30E-12	5.57E-13
Continental Agricultural soil	6.69E-10	6.69E-10	2.19E-10

There were significant differences between the results from EF 3.0/ JRC Supplementary materials and the result produced on USEtox with our input data, but surprisingly, there were also some differences between results shared by JRC and the results we obtained by using the same input data from the same supplementary materials for both substances.

4. Discussion

4.1 Overview of comparison between RA and LCA

Although RA and LCA both follow a well-structured methodological framework with several analytical steps and support decision making for chemical risk management, they largely differ in terms of uses and scope. The scope of most of the LCIA tools covers associated emissions for both human health and ecotoxicity throughout a product's life cycle. Nevertheless, LCA has the scope to focus more on environmental and chemical footprints while RA emphasizes mostly human health hazards. This variability in scope also distinguishes the specialization areas of the users and developers (40).

The current project mostly focused on "Hazard Assessment" and discussed briefly about Risk Characterization. LCA also follows the steps of Hazard and Exposure Assessment, but instead of Risk Characterization, "Impact Assessment" is used. While traditional RA calculates DNEL

as the last step of hazard assessment, LCA calculates CF. But unlike DNEL from traditional RA, CF already considers potential exposure. Another large difference is that DNEL describes the safe level of the substance for humans, whereas CF tells us about the increase in disease cases for per kg emission of that substance.

Where the traditional RA has focused itself to set a margin of safety or health-based guidance values for human health and environmental risk, LCA is focused on comparing between or among products and processes in terms of environmental impacts. LCA can help to get impact scores per impact category which allows us to find the "hot spots", i.e. activities contributing more to the total potential impact (25). Industries can then make active decisions to reduce potential impact by re-designing, choosing alternative materials, other end-of-life options, selecting other suppliers etc. In this way, LCA can contribute to choosing more environmentally-friendly products and also to substituting hazardous chemicals with less hazardous ones. The inclusion of all the relevant impact category indicators gives the decision maker a chance to weigh in several aspects and reduce the risk of problem shifting (e.g. a chemical could be extremely useful in electrification of society and thus good for climate change action but could have detrimental toxicity effects somewhere in the life cycle). LCA also has the possibility to find risks other than those covered by the CSA risk assessment, such as chemicals in lower tonnage bands (<1 ton per year), or from emissions upstream or downstream outside EU.

Not only the fact that many new chemicals enter the supply chain every year, but also our understanding of the complexity of properties and environmental impact of chemicals still deal with a lot of uncertainties regarding data on emissions, exposure pathways, and effects. This makes chemical and carbon footprint assessment a crucial indicator of chemical pollution (7). Carbon footprint is calculated by the aggregated measurement of the global warming potential of six greenhouse gas emissions throughout the life cycle of a product (41). Thus, LCA could help reduce both chemical and carbon footprint and subsequently maintain sustainable chemical management (14). Considering the urgent need to reduce chemical footprint, a Life cycle-based approach for toxicity assessment might be a way to reduce the adverse impact of products on the environment as well as human health (17).

As hazardous chemicals are being released continuously throughout the life cycle of products may end up harming both humans and the environment (14), it is important to integrate safety and sustainability. The concept of safe and sustainable by design (SSbD) might be considered

as a driver for change in this case. The SSbD is an approach with a focus that the product minimizes its harmful impact on both humans and environment but still functions as intended throughout the process starting from the design of the product towards the development, production, use and end of life. It not only facilitates a climate-neutral and resource-efficient economy, but also reduces the environmental and chemical footprint of the products from a lifecycle perspective (42) which will require consideration of impacts along the entire life cycle in the framework (7).

4.2 Data input parameters in RA and PEF

Regarding human health risk assessment of chemicals, data quality as well as proper use of available data is crucial. As this project aimed to compare the input data between the tier 1 exposure modelling for RA and PEF for LCA, it was noticed that USEtox had significantly more mandatory data requirement than the RA. However, high tier models of RA would have more data requirements. Not all data was available on the REACH-IUCLID database, so some data had to be gathered from other software tools, such as EPI SUITE and CompTox. Furthermore, not all parameters were measured under the same conditions; i.e REACH-IUCLID database had data on Vapor Pressure at 20˚C whereas USEtox required this data as Vapour Pressure at 25˚C. The JRC Supplementary input data show a slightly greater value of Vapour Pressure, which can be assumed as being extrapolated from REACH data as per JRC TGD. Here the advantage of CHESAR is that unlike USEtox model, where parameters are fixed with a particular temperature (25˚C), CHESAR is more flexible with the data input as manual input of temperature is allowed. On CHESAR, it is possible to input the experimental data directly without the need of conversion or extrapolation from one temperature to another. It was also noticed that it is sometimes possible for some input parameters to choose units among a few options on CHESAR, but the units are fixed for USEtox input parameters. For example, for water solubility it is flexible to use µg/L or mg/L or g/L on CHESAR, but the unit for water solubility should be mg/L on USEtox. That is why careful consideration is needed when using the data from REACH-IUCLID database in the USEtox model.

For distribution and transformation properties or plainly described as "Fate properties" of substances, biodegradation in air, water, sediment and soil are considered. The fate properties are not mandatory on CHESAR for ECETOC TRA or for human health risk assessment but is mandatory for EUSES or for environmental risk assessment. However, the data on "Degradation rate in air" is mandatory on the USEtox model but cannot be collected from REACH database, rather it has to be calculated from some other data sources where the data

on atmospheric hydroxylation rate is available and then the calculation follows an equation as per USEtox manual (28). For degradation in soil, sediment and water, default values are used on USEtox according to the biodegradation categories assigned on the REACH-IUCLID database, based on experimental testing of e.g. ready biodegradability. While half-lives are reported as number or range of days on CHESAR through screening or simulation tests, USEtox as per JRC TGD uses default values using 1/s as unit. For Bioaccumulation factors, as described in the "Results" section, CHESAR only considers fish, aquatic and terrestrial species, but USEtox tries to consider other ingestions by humans such as meat, milk, leaves and roots which can be estimated based on the Kow if data are not available.

4.3 Comparison between AFs and CnFs

The toxicity study data and assessment factors or conversion factors can be discussed together here. As known, REACH is still limited to using *in vivo* experimental data for human health risk assessment. Repeated dose toxicity is considered as the most sensitive endpoint and the preferred dose descriptor is NOAEL/ NOAEC. If in some cases, NOAEL cannot be determined, LOAEL is used. As REACH usually establishes human health-based guidance values based on animal experimental data, AFs need to be chosen very carefully to reach human equivalent endpoints.

As described earlier, DNEL defines safe exposure levels for humans. DNEL is reported on CHESAR following Equation No. 3 where dose descriptors are divided by AFs (40). The following points should be considered for AFs:

- Dose-response relationship (If NOAEL is not available)
- Interspecies extrapolation (allometric scaling factor and remaining differences);
- Duration of exposure (short term to long term exposure);
- Intraspecies variability;
- Nature and severity of effect;
- Quality of the database (29).

Intraspecies differences deal with the heterogeneity of sensitivity in the human population (e.g.; general population consist of more sensitive population and are continuously exposed in relation to workers) whereas interspecies difference is for species differences between the experimental animal and humans (e.g.; difference of mechanism of action between rats and

humans). Both intraspecies and interspecies variability are subdivided into toxicokinetics and toxicodynamics (29). Toxicodynamics describes the toxic effect of a chemical on the body while toxicokinetics describes the ADME (absorption, distribution, metabolism and elimination) properties on the biological system following exposure of a chemical.

On the other hand, JRC TGD has CnFs for dose descriptor named "$CnF_{referencepoint}$" to convert NOAEL/LOAEL from REACH-IUCLID database to ED_{50} and "$CnF_{endpoint}$" to convert the exposure duration of the studies to chronic study and uses the allometric scaling factors (toxicokinetic) for interspecies differences. LCIA neither accounts for "Intraspecies Difference" nor for the toxicodynamic differences between species. Unlike AFs, the CnFs are not introduced to consider uncertainty in relation to species, effects or durations tested, it is merely intended as a "translation" from one measurement to another. In addition, equal severity is assumed for both cancer and non-cancer effects for LCIA and thus severity is missing as a factor in LCIA.

4.4 Calculation of CFs and EFs

The ED50 was considered significantly more robust compared to NOAEL by the model developers. But solely using a conversion factor of 9 to convert NOAEL to ED50 neither accounts for additional uncertainties, nor does is account for the non-monotonic dose response. Being based on the linear part of a sigmoid dose response curve, this also leaves some room for debate. It needs further investigation if the model was also built with the purpose to make the HTP equivalent to the impact on Aquatic Freshwater Ecotoxicity. The fact is that the perception of ecotoxicity and human health hazard is quite different from the toxicological point of view. As it may seem, the ecosystem can recover from a temporary species loss and that is why the value for ecotoxicity where 50% of the population is being decimated or affected can be accepted but the same value seems rather crude for humans. There has been conversations around if the ED50 will be switched to ED10 for human toxicity non-cancer (43), but the USEtox model in version 2 is still using ED50. Again, there is lack of definition regarding what type of "adverse" effect is to be included in LCIA. The CF calculated in the USEtox model circles around disability and disease, but it might be difficult to relate toxicological endpoint to the non-cancer disability/disease.

Moreover, USEtox does not differentiate between local or systemic toxicity and only picks the lowest NOAEL on REACH-IUCLID database (33, 36). Sometimes, the lowest NOAEL on REACH might not even be human relevant as noted in the current project for substance "X".

Selecting only the lowest NOAEL without considering the human relevance of data might not always be a good idea. The challenge of working across discipline could also be considered here. An LCA operator not having sufficient knowledge on toxicity data might have a deviated choice of human toxicity data which can lead to an error in the calculation of CFs subsequently. Enough guidance on selection and calculation of toxicity data might be a way out. Another factor to be considered is that USEtox takes into account only indirect routes of exposure (e.g. oral and inhalation through environment). Dermal exposure is not considered at all on USEtox version 2.0. In addition, as USEtox was originally designed for organic substances and the multimedia fate modelling is not considered appropriate for inorganics or metals, a default robustness factors must be used for these types of substances for PEF as per JRC TGD (33).

As discussed earlier, while comparing my input data with JRC supplementary materials, significant differences were seen, especially in the ED_{50} values. Even after repeated careful calculations following the JRC TGD and verifying them with relevant personnels involved, the same values were obtained. In the end, a decision was made to contact JRC. It was confirmed by the responsible person at JRC that our calculation was correct. They also stated that JRC noted discrepancies in the calculation of toxicity data and CFs for some substances and are working on updating them.

It was evident while using the USEtox model that it was very sensitive to the data input, especially toxicity data and degradation rate (44). A small change in the data input on USEtox could lead to a magnitude of difference in the calculation of the CFs. It is no surprise that there was a significant difference between the result produced by JRC and the result we produced as the difference between the ED50 data were significant. But it was surprising that even with the same input of the data collected from JRC supplementary material, a slightly different result was produced. But following our contact with JRC, it was discovered that the JRC had used USEtox version 2.1 while we used USEtox version 2.13 corrective release. However, the idea that using a different version or updated version of the same model will generate different results seems a bit concerning. Furthermore, it would be relevant to see a sensitivity analysis showing what is driving the differences.

From the results of both substances, it can also be seen that the lower EF for substance "Y" compared to substance "X" affects the CFs, but the CFs not being consistently lower also proves that fate properties play a role here. Finally, the end result of LCA or the Impact Score needs to be interpreted according to the Goal and Scope definition. As LCA also allows to

compare and contrast options considering several impact categories, maybe one of the steps/substances will reduce the ecotoxic impact score but increase the HTP impacts score, the weighing between these two and choosing one option at the end could be critical and subject for expert judgement.

4.5 Applied methodology

CHESAR is the risk assessment tool recommended by ECHA to be used by industries. And among all the LCIA tools available, the "PEF" method is recommended by the European Commission. Also, both CHESAR and PEF use the REACH-IUCLID database as their primary source of data. In this way, it is easier to compare at least some aspects of these two very different risk assessment methods.

CHESAR is a tiered approach and focused on both human as well as environmental health risk assessment. It does not have a lot of mandatory data requirements for tier 1 to perform risk assessment and also easy to use. But the tonnage of production by the industries as well as the life cycle tree on the CHESAR tool are critical and confidential information. On the other hand, LCA allows us to look into substances from more environmental perspective which is needed in some cases. But having a lot of mandatory data requirements for risk assessment and so many methodological steps make it less user-friendly. And the LCI data collected on resources and emissions of the processes/products from the industries are considered confidential.

The comparison was performed based on two plasticizers which are produced by Perstorp AB. This approach of comparing gives the study a strong base and transparency which fulfils the aims of the project to have an overview of comparison as well as the calculation of EFs and CFs. However, none of these substances are classified as hazardous by ECHA. Therefore, it cannot be concluded how the result would have turned out for a substance that is classified as hazardous/PBT. In addition, both are organic mono constituent substances. As the USEtox model used to perform LCIA was originally built for organic substances, and it is also clear from the JRC TGD that mandatory data requirements differ between organic and inorganic substances. So, it could be assumed that the result might be different in the event of comparing these two methods using inorganics/metals as case studies. Finally, due to time constraints, the comparison was done only from the perspective of hazard assessment, it could not be established how the exposure assessment is done in both methods.

4.6 Adverse outcome pathways (AOP)

AOPs could contribute more to the field of risk assessment in terms of predictive toxicology and regulatory decision making. It could help postulate MoA (Mechanism of Action) for chemicals and substances with the same MoA could be identified and grouped. Thus, AOPs help to save resources and additional testing for risk assessment of chemicals. Specific MoAs could be explored by developing *in vitro* test batteries.

As an example, substance "X" in this research project is a phthalate-based plasticizer and is currently under review as "Endocrine disruptors" under ECHA. As the concept of AOP revolves around the idea that if a chemical stressor can induce the molecular initiating event, the other key events and the adverse outcome will follow as well (45), if mechanistic data on toxicological effects for the substances were investigated, it could be helpful to make a decision on the endocrine disrupting chemicals. In the event, the molecular mechanisms of substance "X" could be compared against the molecular initiating events and key events for "estrogen receptor binding" and "androgen receptor antagonism" on the AOP wiki. In the same way, AOPs could also be useful to perform an LCA for HTP impact assessment. AOPs might play a role in defining the "adverse effects" for both cancer and non-cancer effects for LCA.

4.7 Ethical aspects

Only publicly available secondary data were used to produce results for this research project. Although no animal experiment was performed, most of the data used were from *in vivo* experiments which might still be an issue for ethical concern, although the in vivo tests were conducted in GLP compliant laboratories and according to accepted guidelines and international protocols. But the fact that the same experimental data were used for both risk assessment methods gives us the opportunity to understand the similarities and differences between them without the need of generating new data from additional animal experiments. Besides, to keep industrial confidentiality, the names of the substances analyzed were not disclosed in this report.

Although we did not disclose the names of the substances, both are registered at ECHA and all the data used in this project are publicly available. In the attempt of comparing the AFs and CnFs, it was found that CnFs in LCA do not consider data quality or uncertainties which is crucial as this could lead to underestimation or overestimation of the risk posed by a chemical. The result ultimately has a significant impact on the authority's decision making about the substances and subsequently EU people will be affected by the decision. RA has already been

established as transparent, reliable and reproducible risk assessment method, thus LCA was scrutinized for reproducibility from the perspective of ethical concern. Finding the room for improvement in the data selection process for LCA was another ethical aspect of this project.

4.8 Societal perspectives

Appropriate risk assessment is crucial in the modern world where our everyday activities are largely based on thousands of chemicals. Improving and scrutinizing the risk assessment methods currently used by the industries is an important step for that. From that sense, this research project has the potential to serve a great deal in society.

From the sustainability perspective, LCA contributes to the safe and sustainable design of the products as well as helps the industries to choose more environmentally-friendly products and thus helps reduce chemical footprint (42). It is also of importance to move towards the European Green Deal and EU's new chemical strategy from that aspect. In addition, the project is relevant for the achievement of Sustainable Development Goals (SDG)# 3 "Good Health and Well-being" and SDG#12 "Responsible Consumption and Production". The project concerns itself with contributing to environmentally sound management of chemicals throughout their life cycle, in line with internationally agreed frameworks, as well as significantly reducing their release to air, water and soil in order to minimize their adverse impacts on human health and the environment and thus could help us achieve target 12.4. Moreover, it could help reduce mortality from environmental pollution and achieve SDG target 3.9.

4.9 Future Research/Developmental Needs

Exposure assessment is as important as hazard assessment in the event of performing a risk assessment. There is further scope to compare both methods in terms of exposure assessment as it was not explored in this project. Additionally, though the aim and scope of both methods are quite different, there is a possibility that LCA could contribute more to the field of risk assessment. From that perspective, it would be interesting to venture further into:

- If it would be possible for LCA to improve on the tox data and fate modelling.
- The interpretation of LCA could be investigated focusing on Human Toxicity Potential.
- The difference between the final results for both risk assessment methods (specific RCR from CHESAR with IS for a unit process from LCA).
- If it is possible to make LCIA tools more user-friendly.

5. Conclusion

With the concept of analyzing a product from a cradle-to-grave perspective, LCA is a complex method of risk assessment and the data requirement is dense. Another fact that it is very sensitive to data input makes the process even more complex. Moreover, there are several numbers of LCIA tools available and many are used by industries to support decision making. These tools need further scrutinization to ensure their transparency, reproducibility and reliability.

In the comparison of some aspects between LCA and RA, it can be concluded that these two methods are not directly comparable or replaceable. Both serve different purposes in chemical risk assessment. LCA, unlike traditional RA, does not focus on safety but it could assist us to take full responsibility for a product/process by making us well informed. It might not be possible in the current state for LCA to replace traditional RA, but it could be used as a complementary tool to support decisions in order to avoid unnecessary trade-offs.

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