

Partnership for the Assessment of Risks from Chemicals

D8.4

1st Report on the testing and uptake of the SSbD toolbox through use cases

WP 8 – T8.1



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Contributing Participants	AUTH, IVL, RIVM, Empa, UNINA
Responsible author(s)	Fotini Nikiforou /AUTH/ nikiforou.fotini@gmail.com Maja Halling /IVL/ maja.halling@ivl.se Tomas Rydberg /IVL/ tomas.rydberg@ivl.se Rosella Telaretti Leggieri /IVL/ rosella.telaretti@ivl.se Jaco Westra /RIVM/ jaco.westra@rivm.nl Vrishali Subramanian /RIVM/ vrishali.subramanian@rivm.nl Denis Sarigiannis /AUTH/ sarigiannis@auth.gr Spyros Karakitsios /AUTH/ spyros.karakitsios@gmail.com Achilleas Karakoltzidis /AUTH/ karakoltzidis.achilleas@gmail.com Anna Agalliadou /AUTH/ agalliadou@gmail.com Joanke van Dijk /Empa/ joanke.vandijk@empa.ch Ivo Iavicoli /UNINA/ ivo.iavicoli@unina.it Luca Fontana /UNINA/ luca.fontana@unina.it Veruscka Leso /UNINA/ veruscka.leso@unina.it Andrea D'Anna /UNINA/ andrea.danna@unina.it
Co-authors	Evert Bouman /NILU/ eab@nilu.no Émilien Bourgé /NILU/ embo@nilu.no Milena Brouwer-Milovanovic /IVL/ Milena.Milovanovic@ivl.se Annabel Hill /Defra/ Annabel.Hill@defra.gov.uk Therese Kärnman /IVL/ Therese.Karnman@ivl.se Jenny Lindén /IVL/ jenny.linden@ivl.se Araceli Sánchez Jiménez /INSST/ araceli.sanchez@insst.mites.gob.es Kirsi Siivola /TTL/ kirsi.siivola@ttl.fi Martijn van Bodegraven /RIVM/ martijn.van.bodegraven@rivm.nl
Internal Reviewers ²	N/A
External Reviewers ³	Magnus Løfstedt /EEA/ magnus.lofstedt@eea.europa.eu Dr. Philip Marx-Stoelting /BfR/ philip.marx-stoelting@bfr.bund.de
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Abstract

This document reports on the uptake of the PARC SSbD Toolbox and the tools therein, status April 2024. The content covers status of a case study ongoing within PARC WP8 itself, as well as an outlook to other uptake in the EU.

The focus of the case study is to get a first experience with running several selected computational tools and identify important questions for future development of the toolbox. One of the first extensive SSbD case study were performed by JRC, and the present case study attempts to situate the use case in an innovation context by classifying available safety and sustainability tools in the stage gate model. When the use cases are applied in this way, early and late stage model pipelines can be identified that enable testing individual tools as well as preliminary workflow prototypes. The use cases which were selected are a well-known and extensively researched chemical (Bisphenol-A) used in two distinct applications and three potential alternatives including Bisphenol-A itself.

In brief, the idea is to apply a selection of computational tools included in the toolbox to bisphenol A (BPA) and two BPA alternatives, Isosorbide and BPAP. The intention is that the outcome of the study will help us include relevant input into the subsequent versions of the PARC toolbox. Please note that the aim of the case study is not to find an optimal alternative to BPA, but rather to apply the tools and the toolbox and identify challenges of the tool application and toolbox workflow.

Key Words

Safe and Sustainable by Design

Toolbox

BPA alternatives

Polycarbonate

Epoxy resin

BPAP

Isosorbide

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Acronyms

ADI	Applicability Domain Index
AOP	Adverse Outcome Pathway
CERAPP	Collaborative Estrogen Receptor Activity Prediction Project
CMR	Carcinogenic, Mutagenic, or Reprotoxic
DNEL	Derived No-Effect Level
ED	Endocrine Disruption
ERC	Environmental Release Category
FCM	Food Contact Material
LCA	Life Cycle Assessment
LCI	Life Cycle Inventory
LOAEL	Lowest-observed-adverse-effect level
MCDCA	Multi-Criteria Decision Analysis
NAM	New Approach Methodologies
NOAEL	No-observed-adverse-effect level
OCs	Operational Conditions
PNEC	Predicted No-Effect Concentration
PROC	Process Category
PBT	Persistent, Bioaccumulative and Toxic
PC	Polycarbonate
PMT	Persistent, Mobile and Toxic
RA	Risk Assessment
RCR	Risk Characterization Ratio
RMMs	Risk Management Measures
SSbD	Safe and Sustainable by Design
STOT-RE	Specific Target Organ Toxicity – Repeated Exposure
STOT-SE	Specific Target Organ Toxicity – Single Exposure
TDI	Tolerable Daily Intake
TTC	Threshold of Toxicological Concern
QMRF	QSAR Model Reporting Format
QSAR	Quantitative Structure-Activity Relationship
QSPR	Quantitative-Structure-Property-Relationship
vPvB	very Persistent and very Bioaccumulative

Glossary

AOP (Adverse Outcome Pathway)

A conceptual framework for organizing, synthesizing, and presenting specialized scientific knowledge regarding the linkage between perturbation of a specific biological target, pathway, or process by a stressor, and a consequent adverse outcome(s) considered relevant to risk assessment, regulatory decision-making, and/or environmental management.

Endocrine disrupting chemical (EDC).

Substances of very high concern that mimic or inhibit the effects of hormones. (Source: REACH)

Tools

The term “tools” can be understood as a broad concept including various assessment approaches qualitative, as well as quantitative

1. Introduction

The PARC SSbD toolbox aims to assess SSbD steps as envisioned by the EC framework (Caldeira et al., 2022) along the innovation stages (Cooper, 1990, Cooper, 2008). In order to develop the toolbox, it is necessary to assess the applicability of tools for safety and sustainability assessment in an innovation context, as well as ease of application of these tools. The JRC conducted an extensive case study on plasticizer for food contact materials to test the SSbD framework for a data rich scenario (Caldeira et al., 2023). The next important goal in case study testing is to consider the role of innovation in an SSbD case study, starting with availability of basic information (e.g. CAS number) at early innovation stages. Due to lack of access to a real innovation context, we simulated certain aspects of it with a so-called dry run approach. More specifically, the objectives for the testing in the case study were established as:

- Test the applicability of the tools in relation to different stages of innovation
- Understand the complexity of the tools, and their potential role in the SSbD framework and toolbox
- Evaluate and understand how the tools predict hazards/exposure/risks/impacts
- Discuss the prediction accuracy, for example e.g., by scrutinizing the consistency across different tools

1.1. The EC-SSbD approach

In the Chemicals Strategy for Sustainability (CSS) the European Commission formulated the ambition for an environment and economy that are both climate-neutral and toxic-free. An important pathway to reach this goal is through a transition towards Safe and Sustainable by Design (SSbD). The SSbD approach is put forward by the Commission as a pre-market approach that integrates safety and sustainability considerations starting in the early design stages of chemicals and materials, and covering the whole life cycle (Caldeira et al., 2022).

The EU-SSbD approach describes assessment and redesign phases, and covers the whole lifecycle of the chemical or product. The assessment is built up in 5 distinct steps and each step covering a specific aspect of SSbD, which are the following:

- Step 1 – Hazard Assessment
- Step 2 – Human health and safety aspects in the production and processing phase
- Step 3 – Human health and environmental aspects in the final application phase
- Step 4 – Environmental sustainability assessment
- Step 5 – Socioeconomic assessment

The assessment approach incorporates the early development stages of chemicals and materials by linking it to the innovation processes. (Re)design in the EC-SSbD framework is delineated as molecular, product and process design, and eight illustrative redesign principles are provided: material efficiency, minimizing the use of hazardous chemicals/materials, energy efficiency, use of renewable sources, prevention of hazardous emissions, reduction of exposure to hazardous chemical, design for end of life and whole lifecycle consideration.

1.2. The PARC Toolbox

The SSbD assessment process comprises many different aspects and adds up to a complex framework combining methods from existing approaches on chemical risk, sustainability and socio-economic assessment. To this end, PARC is developing a toolbox that supports stakeholders working on SSbD assessments (Sarigiannis et al., 2024a). The main goals of the toolbox are to encompass a structured collection of tools (including models, data, databases and methods) for SSbD and a well-defined workflow for applying the relevant tools throughout the assessment process.

This toolbox is under development and is reaching a first stage of maturity. The toolbox currently comprises *a set of computational* tools (such as Quantitative Structure Activity Relationship – QSAR, exposure and risk assessment models, as well as models, methods and software for Life Cycle Assessment-LCA) that are organized along both the assessment steps from the EU SSbD framework (Caldeira et al., 2022) and the stages of innovation as they are commonly seen in industrial development of chemicals and materials (Figure 1). The tools cover elements of chemical hazard, exposure (worker, consumer, environment), risk (worker, consumer, environment) and environmental sustainability parameters. Additional work is in progress on building a user interface ('wizard') (Sarigiannis et al., 2024b) to guide the user through the SSbD assessment and to make input/output connections among the tools. The current version of the toolbox includes the tools depicted in the following figure, that have been mapped through the five SSbD steps and five innovation stages.

The mapping of tools between the five SSbD steps and the five innovation stages is based on a comprehensive tool review that has been conducted during the first years of the project. The tools have been mapped to illustrate how they can support the SSbD framework and which of the five SSbD steps can be applied to. They have also been mapped to the innovation process, taking into account the stages for which they are more suitable. Most of the tools included in this figure have been developed for later innovation stages, where there is sufficient information about a chemical or material. Nevertheless, the application of some of these tools can be adapted to meet the needs of the different innovation stages. The level and complexity of information required by a tool were also considered in allocating it to a specific innovation stage. Moreover, the mapping includes different types of computational tools, where in most cases they can deliver the same output (e.g., GaBi, SimaPro, openLCA and Brightway2). However, there are also tools included in the same SSbD step and innovation stage that can provide different outputs, while serving the general scope of this step. ASPENplus¹, for example, is a process simulation software that can be used to provide relevant input data for the different LCA software, such as GaBi² or SimaPro³. It should be noted that this list will be further elaborated and enriched with different kinds of tools, in addition to in-silico tools, such as in vitro and omics data.

¹ <https://www.aspentech.com/en/products/engineering/aspem-plus>

² <https://sphera.com/solutions/product-stewardship/life-cycle-assessment-software-and-data/>

³ <https://simapro.com/>

Table 1: Tools included in the case study

<i>Tool/method</i>	<i>Innovation stage</i>	<i>EC SSbD Step</i>	<i>Tool test performed by (org acronym)</i>
JANUS	Stage 1 Ideation	Step 1	IRFMN
Danish Q(S)AR toolbox	Stage 1 Ideation	Step 1	Empa, IRFMN
OECD QSAR toolbox	Stage 2 Scoping	Step 1	ISS / TTL and the Finnish Environment Institute
Oncologic	Stage 2 Scoping	Step 1	ISS
MSC QSAR models	Stage 1 Ideation	Step 1	RISE/SU
VEGA	Stage 1 Ideation	Steps 1, 2 and 3	Empa, IRFMN
EPIsuite	Stage 1 Ideation	Steps 1 and 3	AUTH
Similarity Tool	Stage 1 Ideation	Step 1	Empa
StopTox	Stage 1 Ideation	Step 1	AUTH
INTEGRA	Stage 2 Scoping and 4 Development	Steps 2 and 3	AUTH
VERMEER FCM (included in MERLIN-Expo)	Stage 2 Scoping and 4 Development	Step 3	AUTH
ProScale	Stage 2 Scoping	Step 2, Step 4	IVL
Advanced Reach Tool ART	Stage 3 Business case	Step 2	TTL and the Finnish Environment Institute
Stoffenmanager	Stage 4 Development	Step 2	TTL and the Finnish Environment Institute
ECETOC TRA	Stage 2 Scoping and 4 Development	Step 2	AUTH
Consumer Exposure Model (CEM)	Stage 3 Business case	Step 3	AUTH
ConsExpo	Stage 3 Business case	Step 3	RIVM
SimpleBox	Stage 2 Scoping / Stage 4 Development	Step 3	RIVM/IVL
quasaLCA	Stage 2 Scoping	Step 4	NILU
GABI	Stage 4 Development	Step 4	IVL
Socio- and economic aspects tools: UNEP methodological sheets for sub-categories in social life-cycle assessment	Not determined	Step 5	DEFRA, BUL
PSILCA, Social Hotspot Database (SHB) and Exiomod	Not determined	Step 5	IVL

A main part of this sub-task has been to run through a case study on a specifically defined use case⁴ including selected chemical and relevant alternatives, applying several tools for each SSbD step, in order to try to understand the level of complexity associated with SSbD; as well as the completeness, complementarity or contradiction among and between tools for the same or similar purpose. Questions considered include:

1. What is the overall applicability domain (chemicals) of the toolbox?
2. Which EC SSbD framework endpoints are covered by the tools? Which endpoints predicted by the tools are not included in the EC SSbD framework?
3. What are the gaps in applying the tools?

⁴ The terms 'case study' and 'use case' have an equivalent meaning in the context of this report

4. What is the level of detail of the tools, in terms of the underlying model, input or output?
5. What are potential operational barriers for working with the tools? E.g., is there any input data that is difficult to obtain in order to use the tool?
6. For which innovation stage is/are tool(s) suited?

To a lesser extent, actions have been undertaken to foster uptake of tools in the PARC SSbD toolbox in projects and use cases outside the PARC project.

The tools in the PARC toolbox are applicable in different SSbD steps and in different innovation stages. By mapping the different tools and dividing them according to their applicability in each SSbD Step and innovation stage, it is possible to illustrate how the tools are distributed in the toolbox. By mapping in and out parameters for all tools, these can also be linked together. Several tools predict data that can be fed as input to tools in other SSbD steps. This makes it possible to connect several tools to a modelling pipeline, which can be tested (Section 3.2).

It is important to note the scope of the activities covered in this deliverable: testing specific tools that could meet the requirements of SSbD steps and innovation stages. Model pipelines tested in this deliverable (Section 3.3) should not be confused with the final workflow of SSbD assessment that will be operationalized in the toolbox. The workflow of the SSbD assessment within the PARC toolbox is currently under development, including process aspects (scoping, assessment, tradeoffs), technically appropriate combination of safety and sustainability, etc. Further, operationalization of the SSbD approach is evolving rapidly, and includes not just in silico tools but also New Approach Methodologies (NAMs).

This report is to communicate the status of the work by end Y2 of PARC, which, as indicated above, is dominated by work on the case study. In this deliverable focus will therefore be on the status of the case study including the case study approach and choice of substances (chapter 2), the approach on testing the toolbox (chapter 3), the first results from the case study organized along the steps of the JRC framework (chapter 4), lessons and next steps (chapter 5), other uptake (chapter 6) and current conclusions (chapter 7).

2. Case study Selection, Definition and Testing

Setting up and carrying out an SSbD case study requires insight and knowledge from different fields of expertise and is therefore a complex and laborious undertaking. Therefore, much of the work focused on discussing the right approach to the case study and the interpretation of the various model outcomes. The work is still on-going, but the available results already provide rich insight in a number of practical SSbD questions related to SSbD operationalization and toolbox development.

During May to October 2023 activity leads and participants from T8.1.1, T8.1.2 and T8.1.3 have worked together in working groups to develop the design of the case study. Initially, three working groups were formed: one on selection of use case and alternatives, one on the innovation stages and one on criteria in the EC-defined SSbD framework. The key ideas from the three groups (which alternatives, stage gate, SSbD criteria) are discussed in the following sections.

2.1. SSbD steps and Innovation stages

Early in the use case discussion it was highlighted that the use case should somehow provide insights about the applicability of different in silico-tools in relation to different innovation stages. The hypothesis was that certain tools are more easily applicable in early stages of innovation, e.g. as they require only limited input of data, and are therefore potentially more applicable for early-stage screening purposes, whereas other tools are more labor and data intensive and therefore more likely to be suitable in later stages.

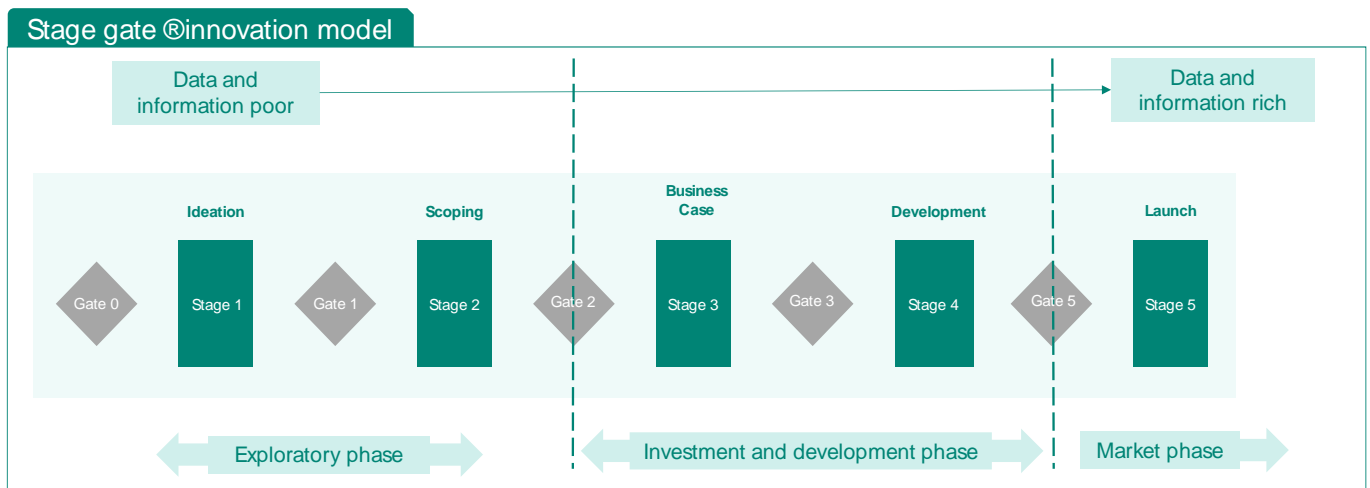


Figure 2: The PARC SSbD team's definition of the innovation stages

2.2. Case study Selection and Definition – The Dry-Run approach

Early in the process but after discussing different options and alternatives, the choice was made to define the approach to test the applicability of different tools and what information they require and provide, by agreeing on a theoretical substitution case with Bisphenol-A (BPA) as the reference chemical. BPA was

chosen as the chemical of focus for the case study as it is being studied extensively also in PARC WP5⁵ and there is a lot of available information on it. The rationale for using such a data rich compound as reference is that this opens up the possibility to track back through the innovation stages to the level of early development, essentially pretending not to have more information than the chemical structure, and comparing the outcome of the model prediction with the actual known and measured data. However, it should be noted that BPA, as a rich-data substance, is included in the training set of many predictive models. Thus, many of the model predictions for BPA are accurate and characterized with good reliability, while in some cases they also include the experimental values of the respective endpoints.

2.2.1. Choice of application

Beyond the selection of the reference chemical, the group discussed relevant applications or uses of BPA to be selected for the case study. BPA-based polymers are lightweight and have become ubiquitous. Polycarbonates application include hard plastics like CD, DVD, food containers, pens and numerous other items use in construction materials, 3D printing, data storage, automotive, aircraft and security components, appliances, consumer, healthcare, medical, and sporting goods. Epoxy resins include paints, internal cans lacquers, use also in electronics (halogenated BPAs) as lacquers in motherboards. Additionally, statistics on the current use of BPA in the market served as the basis for the selection of the tested applications.

It was decided to include two different use case applications in a preliminary screening. Depending on the initial results, including the available identity of alternatives and considerations on the suitability to test the functionality of the SSbD Toolbox it may be decided on a later stage to continue the case study with both use scenarios or to focus on just one of them.

The two initial use case applications were:

1. BPA alternatives in epoxy resins in paint.
2. BPA alternatives in polycarbonate used in reusable water bottles.

2.2.2. Choice of substances as alternatives to BPA

In order to simulate the situation of development of new chemical(s) for particular applications that could be tested for their safety and sustainability performance, a special working group was appointed to decide which alternatives to BPA should be included in the study with the intention to have one alternative with poor data availability and one alternative with intermediate data availability.

The alternatives to BPA should preferably be able to produce materials with similar technical specifications (heat resistant, rigid, durable, transparent). Other bisphenols are known to be used as alternatives to BPA. However, in order to avoid regrettable substitution, there has been an increasing focus on finding non-bisphenol alternatives. In addition, it is desirable to include both data rich and data poor substances in the case study in order to test the applicability of the SSbD toolbox on substances with different levels of existing information.

Criteria for selection of alternatives to BPA to be included in the SSbD case study:

- Produce materials with similar technical specifications (heat resistant, rigid, durable, transparent)
- Include both data rich and data poor alternatives

⁵https://www.eu-parc.eu/sites/default/files/2023-08/PARC_AD5.1.pdf

- Include both bisphenol and non-bisphenol alternatives

Based on the screening, **Isosorbide (CAS RN 652-67-5)** was identified as a suitable alternative to BPA with intermediate information. Being registered as a high tonnage chemical under REACH it is expected that quite a lot of information on toxicological properties is available for the monomer. However, it has not been further explored if any information is available on the presence and release of substances from the polymeric material made from isosorbide.

Bisphenol AP (BPAP) was selected as the first priority for a BPA alternative with poor information to be tested in the case study. This choice was also based on the list of prioritized alternatives to BPA, which was jointly compiled by PARC partners within WP5 and ECHA⁶. This list was derived after a workshop in June 2022 to determine the alternative substances on which PARC should focus, considering both human and environmental health.

Table 2: General Information of the substances used in the case studies.

Name	Acronym	EC	CAS	ECHA dossier	SMILES	Mol. weight
4,4'-isopropylidenediphenol	BPA	201-245-8	80-05-7	https://echa.europa.eu/el/registration-dossier/-/registered-dossier/15752	<chem>CC(C)(C1=CC=C(O)C=C1)C1=CC=C(O)C=C1</chem>	228.28 (g/mol)
1,1-bis(4-hydroxyphenyl)-1-phenylethane	BPAP	433-130-5	1571-75-1	https://echa.europa.eu/el/registration-dossier/-/registered-dossier/9115/1/1	<chem>CC(C1=CC=CC=C1)(C1=CC=C(O)C=C1)C1=CC=C(O)C=C1</chem>	290.36 (g/mol)
1,4:3,6-dianhydro-D-glucitol	Isosorbide	211-492-3	652-67-5	https://echa.europa.eu/el/registration-dossier/-/registered-dossier/5661/1/1	<chem>C1C(C2C(O1)C(CO2)O)O</chem>	146.14 (g/mol)

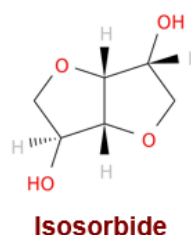
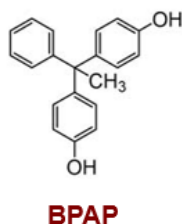
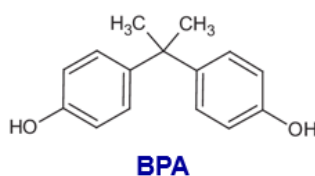


Figure 3: Structure of the substances used in the case studies.

⁶ https://www.eu-parc.eu/sites/default/files/2023-08/PARC_AD5.1.pdf

2.3. Description of applications (uses) and use scenarios for BPA in the case study

The two initial use scenarios were:

1. BPA alternatives in polycarbonate used in reusable water bottles
2. BPA alternatives in epoxy resins in paint

No general assessment scenario for the two use scenarios has been defined initially. As a part of the case study this was left to each individual tool tester when an assessments scenario was needed.

The two BPA uses are further described in the following subsections.

2.3.1. Polycarbonate reusable bottles

To harmonize the research efforts of those involved and provide a common basis and structure for the individual safety and sustainability assessments for SSbD step 4, a system description of the polycarbonate reusable bottle application was developed for BPA and the two alternatives BPAP and Isosorbide.

The functional unit following the LCA plastic method (Commission et al., 2021) was set to the provision of a 0,5-liter bottle for daily use over two years in the entire EU-28 market to an average EU-28 consumer, without leaking or breaking during transport or use. And the geographical scope was defined as follows. Raw material production varies but enters the Rotterdam harbour (NL) and is transported to Chemiepark Gendorf (DE), products are sold and used within Germany, spent products are also processed in Germany or transported to countries according to waste statistics (Eurostat, 2024). It can be noted that these scenarios were designed and developed as an initial work during the tool testing activity for LCA.

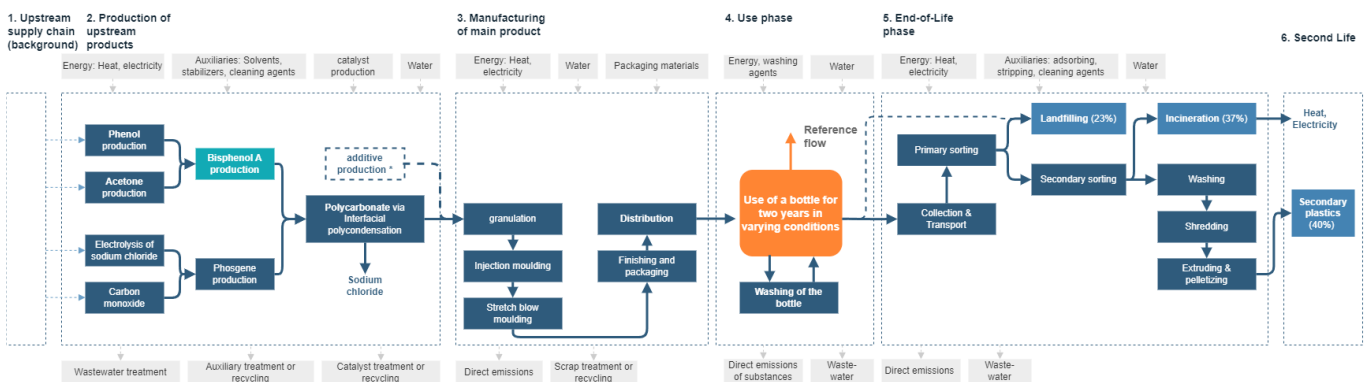


Figure 4: System Description of the polycarbonate reusable bottle application, including production of BPA.

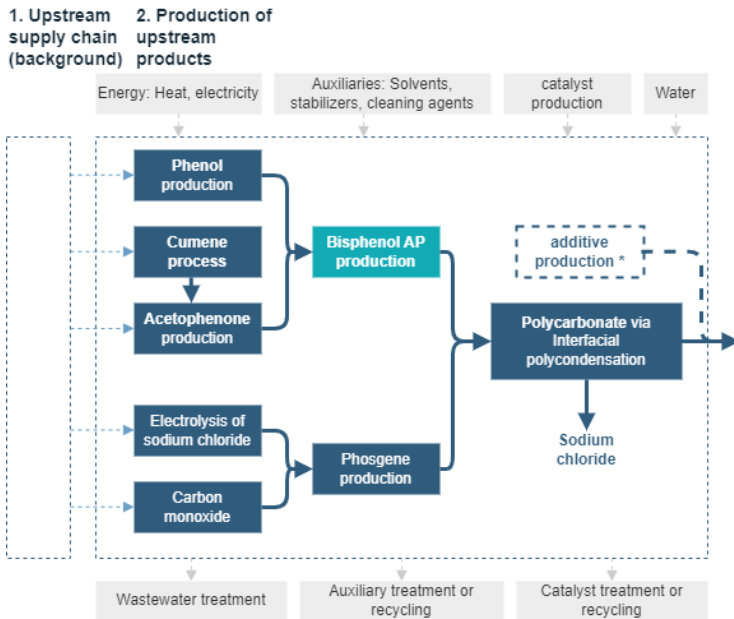


Figure 5. System Description of the production of BPAP.

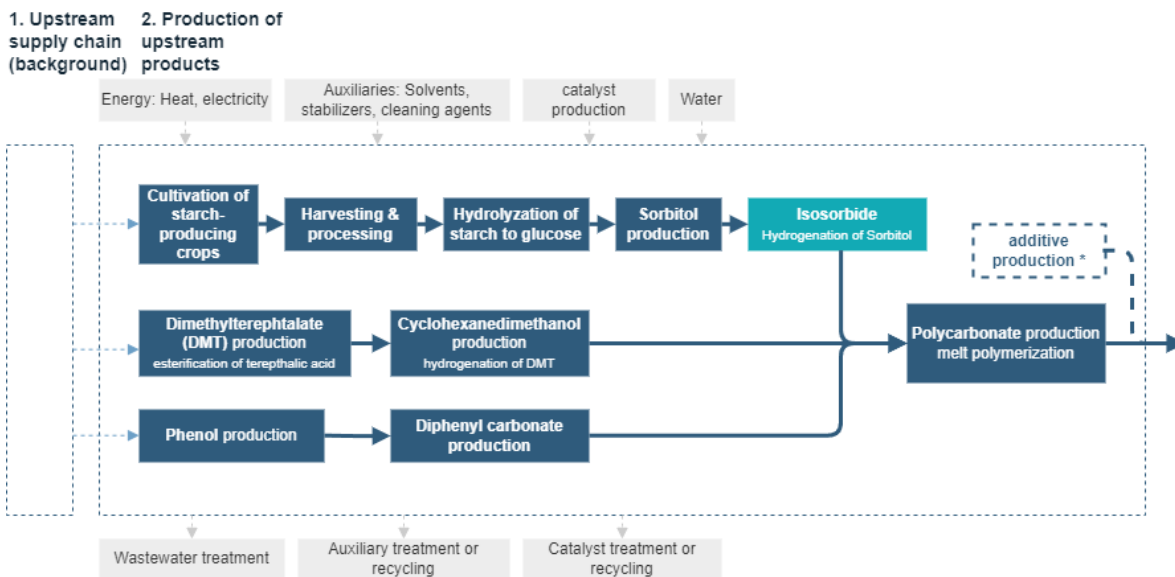


Figure 6: System Description of the production of Isosorbide

2.3.2. Epoxy resins in paints

For now, no general assessment scenario for epoxy resins in paint has been defined. As a part of the case study this was left to each individual tool tester when an assessments scenario was needed.

For example, the following assessment scenario was developed when assessing the tool ConsExpo.

Based on the description of the epoxy paint application, an internet search about consumer uses of epoxy paint, the available models in ConsExpo, and the default scenarios described in the ConsExpo Paint products Fact Sheet, an assessment was constructed that describes home application of epoxy floor paint with two scenarios: exposure during mixing and loading of a two-component epoxy floor paint, and exposure during application of the prepared paint to the floor. Both scenarios contain an inhalation component to evaporation, and a dermal component due to spillage.

3. Testing the SSbD toolbox

3.1. Engaging tool testers

In October and November 2023 there was a call for volunteers to the case study to test specific safety and sustainability tools.

A template and instruction on how to perform the tool testing was distributed by mail to all members of T8.1.3. Please see Appendix for reporting template. By starting with the input of chemical structure and intended application (which is the information that is likely to be available at early stages), the tool testers were asked to investigate what additional information might be needed to be able to run the tools.

The first data was received in mid-November. Tool testing and evaluation was performed until the beginning of February 2024. Data was compiled from the templates filled out by the tool testers – as result of the testing – into a report document. All tool testers were encouraged to fill in input parameters and output endpoints values for the tested tools in designated Excel file. Experimental or measured values were also listed for comparison to the predictions.

In early February 2024 six dedicated task forces were formed, one for each SSbD step, and one overarching transversal taskforce. The task forces consist mainly of the participants who have tested the different tools but also of other experts from the PARC consortium. The task forces have had weekly meetings where the results from the tool testing have been discussed and questions of concern have been identified. Each task force was also asked to focus on a set of questions and identify areas for each step that need specific focus and continued work. The taskforces discussed the following questions:

7. What is the overall applicability domain (chemicals) of the toolbox?
8. Which EC SSbD framework endpoints are covered by the tools? Which endpoints predicted by the tools are not included in the EC SSbD framework?
9. What are the gaps in applying the tools?
10. What is the level of detail of the tools, in terms of the underlying model, input or output?
11. What are potential operational barriers for working with the tools? E.g., is there any input data that is difficult to obtain in order to use the tool?
12. For which innovation stage is/are tool(s) suited?

The taskforces were also asked to assess the results from the different tools within each SSbD step.

- a) Comparison of tools: is the outcome consistent among different models within each step?
- b) Is there a valid explanation for this discrepancy?

In this case study we have strived to include tools from all SSbD steps. There has also been an ambition to include as many tools as possible in order to be able to make a comparison between the tools within the same SSbD step. It is important to be aware that the choice of tools is based on which partners that showed interest in participating in the case study. Some tool testers have been actively asked to participate, but no tools have been excluded from the case study.

- Physicochemical properties for multimedia model from VEGA
- Environmental fate properties from EPISuite
- Food contact material migration from VERMEER FCM (included in MERLIN-Expo)
- Paint emissions from Consumer exposure model.

To calculate an overall SSbD score, hazard predictions from QSARs, environmental consumer and dietary exposure data from INTEGRA and occupational exposure from ECETOC TRA were used. Figure 8 illustrates what type of data that feeds into the connecting tools to produce an overall SSbD score in the INTEGRA example.

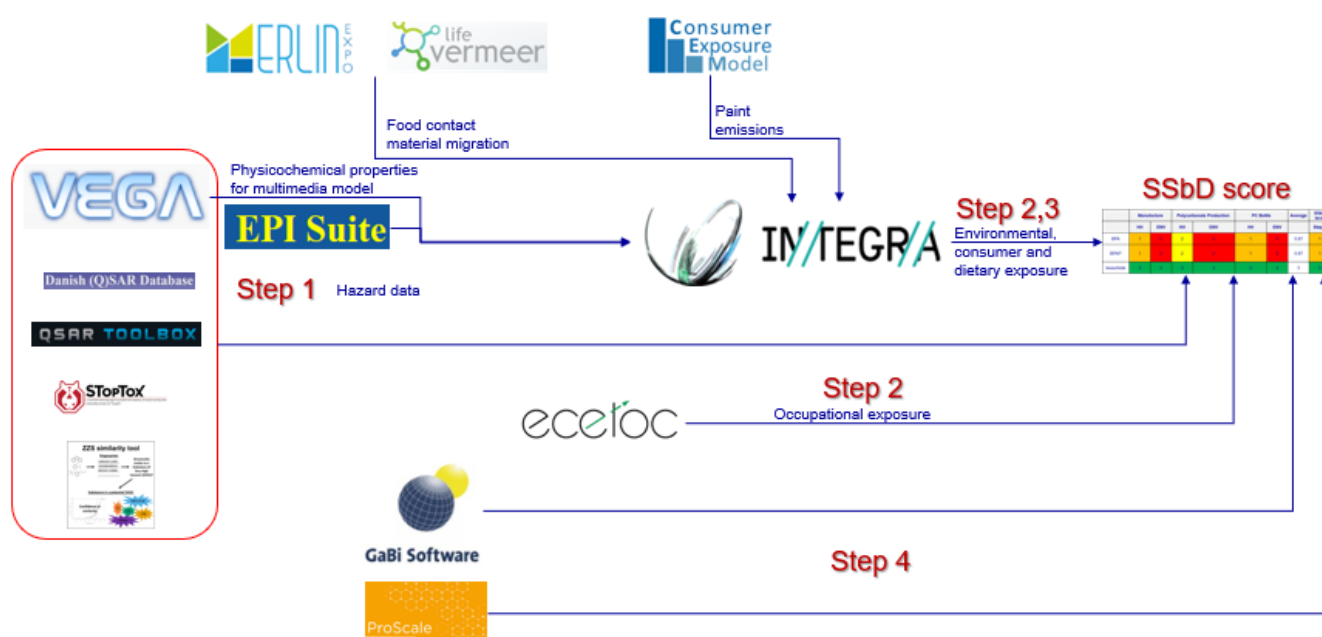


Figure 8: Model pipeline of the case study

3.4. Approach

The present study was conducted during both the early and late stages of innovation to evaluate the efficacy of the toolbox and to identify potential variations in the results. This approach will provide valuable insights into the applicability of the toolbox throughout the innovation process. In more detail, the approach taken included the following aspects:

- **Early stages assessment**

During the assessment in the early stages of innovation only the chemical structure and the application of the substance are known. From this, physicochemical properties can be predicted if needed. The physicochemical properties that can be used to get insight to environmental fate, migration from food contact material (FCM), evaporation from paints and hazards are estimated by Quantitative-Structure-Property-Relationships (QSPRs). Moreover, only basic estimations about the use and the tonnage are available. The environmental emissions are defined by the overall production volume and the respective Environmental Release Categories (ERCs), relevant to the process involved. Thus, the Predicted Environmental Concentrations (PECs) and the respective contribution to other pathways of exposure, such as diet through the food web, will be defined based on that.

- **Late stages assessment**

During the assessment in the late stages of innovation both the chemical structure, detailed application scenario and the experimental and (higher tier) modelled data on hazard, risk and impacts are available. The physicochemical properties and hazard data are retrieved from experimental studies included in databases, such as the ECHA Database and CompTox Chemicals Dashboard. When the data is insufficiently available, QSARs are applied to calculate the respective properties. Regarding the environmental releases, releases to specific media for given processes are used. If not, emissions in the environment are defined by the overall production volume and the respective ERCs, relevant to the process involved.

- **Toxicological thresholds**

During the execution of the case study in the early stages of innovation, the availability of toxicological data was very limited. Thus, the implementation of hazard assessment and the derivation of Risk Characterization Ratios (RCRs) in risk assessment became challenging. In order to overcome this difficulty, we used alternative methods to generate the respective data. The VEGA model was used to predict the required quantitative dose descriptor (No-Observed-Adverse-Effect-Level - NOAEL) for deriving the corresponding toxicological thresholds for the human health risk assessment (Derived No-Effect Level- DNEL and Tolerable Daily Intake – TDI). As the assessment is being conducted at the initial stage of the innovation, with only the chemical structure and the intended application being known, this approach has been employed to offer initial screening results for mitigating the potential chemical risks. Further refinement is possible, for instance considering the VEGA model for the Lowest-Adverse-Effect-Level – LOAEL, comparing the range between the NOAEL and the LOAEL. In addition, the information regarding the applicability domain index (ADI) provided by VEGA, becomes a critical aspect in particular for this endpoint (NOAEL), which is a difficult one, due to the complexity of the toxicological mechanisms, the lack of data, and the uncertainty associated to the protocol to define the value. In practice, it is recommendable to prefer predictions with high reliability as indicated by the ADI value), looking for the presence of similar, related compounds, as indicated by VEGA. This aspect is of course closely related to the use of read-across, which should complement in silico models in general, within a weight-of-evidence approach, and this applies in particular for the "difficult" cases. Due to time constraints and based on the stage of innovation, the QSAR predictions were not further evaluated at this stage. For the current case study, a read-across approach was not part of the assessment, but it is being considered as a future course of action.

In the late innovation stage, the availability of toxicological data for BPAP is quite limited. Moreover, there are no registered toxicological thresholds for BPAP, as well as a limited number of toxicological studies. Therefore, the same toxicological thresholds as for the early stage innovation were adopted. In terms of environmental risk assessment in early innovation, the respective toxicological thresholds (Predicted No-Effect Concentrations, PNECs), were predicted using ECOSAR QSAR model and the Equilibrium Partitioning Method (EPM). In more detail, ECOSAR was used for deriving the PNEC for water (freshwater and marine water), where the lowest chronic value for freshwater species was divided by the assessment factor of 10. On the other hand, the PNEC for sediment (freshwater and marine water) and soil were calculated by EPM. The approach followed for the reference values and the respective values are described in the tables below (Table 3 and Table 4).

Table 3: Reference values calculation

Chemicals	DNELs			TDIs			PNECs		
	Value	Source	Justification	Value	Source	Justification	Value	Source	Justification
<i>BPA</i>	Available	ECHA Dossier	-	Available	EFSA	-	Available	ECHA Dossier	
<i>BPAP</i>	Lack of data	QSARs	NOAEL value obtained from VEGA	Lack of data	QSARs	NOAEL value obtained from VEGA	Lack of data	QSARs and EPM*	ECOSAR is used for PNEC for water derivation; EPM used for PNEC for sediment and soil
<i>Isosorbide</i>	Lack of DNEL for inhalation	ECHA Dossier	NOAEL value from ECHA	Lack of data	ECHA Dossier	NOAEL value from ECHA	Available	ECHA dossier	-

*EPM: Equilibrium Partitioning Method

Table 4: Reference values in early and late innovation stages

Reference value	BPA DNELs		BPAP DNELs		Isosorbide DNELs	
	Early Innovation	Late Innovation	Early Innovation	Late Innovation	Early Innovation	Late Innovation
<i>Worker Inhalation (mg/m³)</i>	0.138	2	0.19		12.88	165.23
<i>Worker Dermal (mg/kg bw day)</i>	0.039	0.066	0.055		3.65	697.29
<i>Consumer Inhalation (mg/m³)</i>	0.25	1	0.35		23.19	297.5
Reference value	TDIs					
Innovation stages	Early Innovation	Late Innovation	Early Innovation	Late Innovation	Early Innovation	Late Innovation
<i>(mg/kg)</i>	0.043	0.0000002	0.06		3.91	33.47
Reference value	PNECs					
Innovation stages	Early Innovation	Late Innovation	Early Innovation	Late Innovation	Early Innovation	Late Innovation
<i>Freshwater (mg/l)</i>	0.027	0.023	0.011		75.47	0.107
<i>Marine Water (mg/l)</i>	0.0023	0.019	0.001		7.5	0.011
<i>Freshwater sediment (mg/kg sediment dw)</i>	0.6405	1.2	2.121		59.49	0.4
<i>Marine water sediment (mg/kg sediment dw)</i>	0.064	0.24	0.213		5.95	0.04
<i>Soil (mg/kg soil dw)</i>	0.508	3.7	1.719		9.22	0.016

4. Results, one example of model pipeline

4.1 Step 1 – Hazard Assessment

During early stages of innovation, there were no available hazard data for the chemicals except for their chemical structure and intended application. To define the hazard properties of the chemicals addressed in Step 1 of the SSbD framework, several QSAR models were employed. By entering the SMILES code of the chemical as the only required input, QSARs can provide predictions about hazard properties, such as carcinogenicity, mutagenicity, reproductive toxicity and endocrine disruption. At this stage, no further evaluation of the predictions' reliability was carried out, apart from considering the applicability domain of each prediction.

4.1.1 Structural similarity

BPA, BPAP and Isosorbide were cross-referenced against multiple lists of substances of concern to check whether they were already flagged as a chemical of concern (Table 5). For this step, a CAS number is required as input. Presence of the chemical on any of the substance of concern lists indicates that the hazards of a chemical are already assessed. Next, the structural similarity to known substances of concern was assessed using the ZZS similarity tool (Table 5), necessitating the input of the structure in SMILES format. In the context of similarity assessments, a decision must be made to ascertain when a structure bears sufficient resemblance to a known substance of concern, indicating a high likelihood of similar adverse effects. Based on the structural similarity to known substances of concern, the user may either 1) identify specific endpoints that require further experimental testing or 2) opt to halt the SSbD assessment process. Even though a high similarity is found for both BPAP and Isosorbide to known SVHCs and BPAP is already present on a regulatory list due to its long-term hazardous effect on the environment, the SSbD assessment is continued for all substances for the sake of this case-study.

Table 5: Structural similarity of chosen substances using ZZS similarity tool.

Substance	Presence on regulatory lists	Structural similarity to known chemicals of concern (ZZS similarity tool)
BPA	Yes: for ED properties	-
BPAP	Yes: for environmentally hazardous long-term effects	CMR 1A/1B: 93% similarity to BPA (CAS 80-05-7); 67% similarity to 4,4-isobutylethylidenediphenol (CAS 6807-17-6) ED substances: 88% similarity to BPA (CAS 80-05-7)
Isosorbide	No	CMR 1A/1B: 60% similarity with tetrahydro-2-furylmethanol (CAS 97-99-4)

4.1.2 Human Health hazards

4.1.2.1 Early Innovation

Several models were employed to predict the human health endpoints (using only the chemical structure – SMILES code) as proposed by JRC (Caldeira et al., 2022), including VEGA⁷, Danish (Q)SAR Database⁸,

⁷ <https://www.vegahub.eu/portfolio-item/vega-qsar/>

⁸ <https://qsar.food.dtu.dk/>

OECD QSAR Toolbox⁹ and StopTox¹⁰. This list is preliminary and not exclusive. Considerations regarding this inclusion list are ones, related to the easiness of implementation, and general ones, related to transparency, details in the information provided by the model, full access of the model documentation on a technical/IT point of view and formal point of view, such as QSAR Model Reporting Format (QMRF), possibility for the user to have full access to the supporting documentation, including the training set of the model, allowing the use for read-across.

More precisely, VEGA was the tool that was used for the prediction of most of the endpoints. There are several models available in VEGA for the same endpoint. The platform offers the result of the combined evaluation of these individual models in the case of mutagenicity. In this case study, the outcomes of the so-called consensus model were utilized. As a precautionary measure, the worst-case value was chosen when there were several model predictions that fell inside the applicability domain for the other parameters. Specifically, VEGA was used for the prediction of the following endpoints: carcinogenicity, mutagenicity, reproductive toxicity, endocrine disruption-human health (ED-HH), acute oral toxicity, skin sensitization, skin and eye irritation. For ambiguous or unreliable predictions, additional tools were used for the relevant endpoints when available. Specifically for BPAP, the Danish (Q)SAR Database was utilized to predict reproductive toxicity and skin sensitization. Additionally, for both BPA and BPAP, the SToxTox tool was employed to provide predictions for skin and eye irritation. Finally, Janus and Danish (Q)SAR Database were applied for the prediction of reproductive toxicity of Isosorbide. Janus¹¹ is included in VEGA Hub and is based on the same approach with VEGA, combining the results from several VEGA models into a single output and its overall reliability. A more detailed and integrated approach will be described in the full BPA case study report.

Moreover, Danish (Q)SAR Database was used for the prediction of respiratory sensitization and StopTox, for the prediction of dermal and inhalation acute toxicity. Regarding the aspiration toxicity hazard, the prediction was not based on QSARs as no relevant model was identified for this endpoint. A substance is classified in the aspiration toxicity category if it is a hydrocarbon and has a specific kinematic viscosity value. The target chemicals in question are not hydrocarbons, hence they do not fall within this category. Regarding the prediction of respiratory sensitization for Isosorbide, the results were inconclusive (as shown in Table 6). We only considered the model predictions that fall within the model's applicability domain (CASE Ultra and SciQSAR). One of the predictions is positive while the other is negative. This arises from the fact that these QSARs include different molecular descriptors and they have been based on different algorithms. Finally, there are data gaps in the prediction of STOT-RE and STOT-SE, as no relevant QSAR models were identified for these endpoints.

Table 6: Human Health - Early innovation

Chemicals	Human health hazards													
	Carcinogenicity	Mutagenicity	Reproductive toxicity	ED (HH)	Respiratory sensitization	STOT-RE	Skin sensitization	Acute toxicity - oral	Acute toxicity - dermal	Acute toxicity - inhalation	Skin corrosion/irritation	Eye damage/irritation	Aspiration hazard	STOT-SE
BPA	NEG	NEG	POS	POS	POS	MISS	POS	POS	POS	NEG	POS	POS	NEG	MISS
BPAP	NEG	NEG	POS	POS	POS	MISS	POS	NEG	POS	NEG	POS	POS	NEG	MISS

⁹ <https://qsartoolbox.org/>

¹⁰ <https://stoptox.mml.unc.edu/>

¹¹ <https://www.vegahub.eu/portfolio-item/janus/>

Isosorbide	NEG	NEG	NEG	NEG	INC	MISS	NEG	NEG	NEG	NEG	NEG	NEG	NEG	MISS
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Table 7: Color coding explanation

POS	Positive prediction
NEG	Negative prediction
MISS	Data Missing
INC	Inconclusive results

4.1.2.2 Late Innovation

In late innovation, the classification of the three substances was based on harmonized classification (Classification and Labelling Inventory), self-classification (ECHA database and their REACH dossiers) and the Candidate List of Substances of Very High Concern (SVHC) (Tables 8, 11 and 13). BPA is fully registered, but data is missing for the other two, making their classification unclear.

Table 8: Human Health Hazards - Late Innovation

Chemicals	Human health hazards													
	Carcinogenicity	Mutagenicity	Reproductive toxicity	ED (HH)	Respiratory sensitization	STOT-RE	Skin sensitization	Acute toxicity - oral	Acute toxicity - dermal	Acute toxicity - inhalation	Skin corrosion/irritation	Eye damage/irritation	Aspiration hazard	STOT-SE
BPA	NC	NC	Repr. 1B	POS	NC	NC	Skin Sens. 1	NC	NC	NC	NC	Eye Dam. 1	NC	STOT-SE 3
BPAP	MISS	MISS	MISS	MISS	MISS	MISS	NC	NC	NC	MISS	NC	NC	MISS	MISS
Isosorbide	MISS	NC	NC	NC	MISS	NC	NC	NC	NC	NC	NC	NC	MISS	MISS

Table 9: Color coding explanation

XXX	Classified XXX according to CLP criteria, identified as SVHC
NC	Not classified according to CLP criteria
MISS	Data Missing

4.1.3 Environmental hazards

4.1.3.1 Early Innovation

The VEGA model was used to determine environmental hazards, except for endocrine disruption (for the environment) and ozone layer hazards, where no relevant QSAR models were identified. VEGA has models for estrogen receptors (related to binding to the receptors and further steps, as within the Collaborative Estrogen Receptor Activity Prediction Project (CERAPP) scheme), androgen receptor (as within the COMPARA scheme), thyroid receptor (alpha and beta), thyroid peroxidase inhibitory activity, and steroidogenesis (aromatase). There is also a general model for endocrine activity, related to the lists of substances from the EC and WHO. In the near future models will be added for steroidogenesis. In order to make a final assessment, VEGA was used to individually predict Persistence, Bioaccumulation and Toxicity (PBT) and Persistence, Mobility and Toxicity (PMT) parameters. The results are presented in the table (Table 10) below.

Table 10: Environmental hazards – Early Innovation

Chemicals	Environmental hazards					
	PBT/vPvB	PMT/vPvM	ED (ENV)	Ozone	Chronic aquatic toxicity	Acute aquatic toxicity
BPA	NEG	NEG	MISS	MISS	POS	POS
BPAP	NEG	NEG	MISS	MISS	POS	POS
Isosorbide	NEG	NEG	MISS	MISS	NEG	NEG

4.1.3.2 Late Innovation

In late innovation, the classification of the three substances was based on harmonized classification (Classification and Labelling Inventory), self-classification (ECHA database and their REACH dossiers) and the Candidate List of Substances of Very High Concern (SVHC). For BPA, the assessment for Persistence, Mobility and Toxicity (PMT) was based on available reports for existing assessments (UBA, 2019, UBA, 2023). Regarding BPAP and Isosorbide, data is missing for most of the endpoints, as shown in the table below.

Table 11: Environmental hazards – Late Innovation

Chemicals	Environmental hazards					
	PBT/vPvB	PMT/vPvM	ED (ENV)	Ozone	Chronic aquatic toxicity	Acute aquatic toxicity
BPA	NEG	NEG	POS	MISS	Aquatic Chronic 1	Aquatic Acute 1
BPAP	MISS	MISS	MISS	MISS	Aquatic Chronic 1	Aquatic Acute 1
Isosorbide	MISS	MISS	MISS	MISS	NC	NC

4.1.4 Physical Hazards

4.1.4.1 Early Innovation

During the early innovation, data gaps were identified in the physical hazard endpoints. More specifically, no relevant QSAR models were identified that can predict the specified endpoints.

Table 12: Physical hazards – Early Innovation

Chemicals	Physical hazards											
	Explosives	Flammable	Aerosols	Oxidizing	Gases under pressure	Self-reactive	Pyrophoric liquids, solids	Self-heating	Emits flammable gas	Organic peroxides	Corrosivity	Desensitized explosives
BPA	MISS	MISS	MISS	MISS	MISS	MISS	MISS	MISS	MISS	MISS	MISS	MISS
BPAP	MISS	MISS	MISS	MISS	MISS	MISS	MISS	MISS	MISS	MISS	MISS	MISS
Isosorbide	MISS	MISS	MISS	MISS	MISS	MISS	MISS	MISS	MISS	MISS	MISS	MISS

4.1.4.2 Late Innovation

Additionally, lack of physical hazard data was also observed in late innovation (Table 13).

Table 13: Physical hazards – Late Innovation

Chemicals	Physical hazards											
	Explosives	Flammable	Aerosols	Oxidizing	Gases under pressure	Self-reactive	Pyrophoric liquids, solids	Self-heating	Emits flammable gas	Organic peroxides	Corrosivity	Desensitized explosives
BPA	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
BPAP	NC	NC	NC	NC	NC	MISS	MISS	MISS	NC	MISS	MISS	MISS
Isosorbide	NC	NC	MISS	NC	MISS	MISS	MISS	NC	MISS	MISS	MISS	MISS

4.1.5 Data gap filling

To fill the data gaps occurred in late innovation for both human health and environmental hazards, we applied the following approaches, as shown in Tables 13 and 14:

Justification on lack of data:

- BPAP: Carcinogenicity, Mutagenicity, Reproductive toxicity, Respiratory sensitization, Acute toxicity inhalation: these data gaps were filled using QSAR predictions.
- Isosorbide: Carcinogenicity, Respiratory sensitization and STOT-SE were filled using information from available safety datasheet.
- Endocrine disruption – human health (HH):
 - BPA was identified as an endocrine disruptor for HH based on the DEDuct¹² and TEDX¹³ lists for ED properties.
 - BPA was identified as an endocrine disruptor for HH based on the DEDuct¹⁴ and TEDX¹⁵ lists for ED properties.
 - Isosorbide has not been proposed for the assessment, nor has been identified in any of the ED lists. No indication of endocrine activity was identified from the predictive in silico tools. Therefore, it is not considered as a potential endocrine disruptor for HH.
- Aspiration toxicity: there are data gaps in the classification of BPAP and Isosorbide. A substance is classified in aspiration toxicity category if it is a hydrocarbon and has a specific kinematic viscosity value. But since these substances aren't hydrocarbons, they do not fall within this category.

¹² <https://cb.imsc.res.in/deduct/home>

¹³ <https://endocrinedisruption.org/interactive-tools/tedx-list-of-potential-endocrine-disruptors/search-the-tedx-list>

¹⁴ <https://cb.imsc.res.in/deduct/home>

¹⁵ <https://endocrinedisruption.org/interactive-tools/tedx-list-of-potential-endocrine-disruptors/search-the-tedx-list>

Table 14: Human Health Hazards – Data gap filling

Chemicals	Human health hazards													
	Carcinogenicity	Mutagenicity	Reproductive toxicity	ED (HH)	Respiratory sensitization	STOT-RE	Skin sensitization	Acute toxicity – oral	Acute toxicity – dermal	Acute toxicity – inhalation	Skin corrosion/irritation	Eye damage/irritation	Aspiration hazard	STOT-SE
BPA	NC	NC	Repr. 1B	POS	NC	NC	Skin Sens. 1	NC	NC	NC	NC	Eye Dam. 1	NC	STOT-SE 3
BPAP	NEG	NEG	POS	POS	POS	MISS	NC	NC	NC	NEG	NC	NC	NC	MISS
Isosorbide	NEG	NC	NC	NC	NEG	NC	NC	NC	NC	NC	NC	NC	NC	NEG

Justification on lack of data:

- Hazardous to the ozone layer: None of the substances is listed on the list of ozone-depleting substances (Annex I to Regulation 1005/2009). Thus, they are not classified as hazardous to the ozone layer.
- Endocrine disruption – environment (ED ENV): based on ECHA (ECHA, 2023), BPA has been identified as ED for both the human health (HH) and the environment (ED). The other two substances, BPAP and Isosorbide, have not been proposed for the assessment. Therefore, there haven't been identified as ED for HH and ENV.

Table 15: Environmental Hazards – Data Gap Filling

Chemicals	Environmental hazards					
	PBT/vPvB	PMT/vPvM	ED (env)	Ozone	Chronic aquatic toxicity	Acute aquatic toxicity
BPA	NEG	NEG	POS	NC	Aquatic Chronic 1	Aquatic Acute 1
BPAP	NEG	NEG	NP	NC	Aquatic Chronic 1	Aquatic Acute 1
Isosorbide	NEG	NEG	NP	NC	NEG	NEG

In the context of physical hazards, only the endpoint of desensitized explosives could be filled. In more detail, none of the substances is classified as explosive. Thus, they are not applicable to this endpoint, as well.

Table 16: Physical Hazards – Data Gap Filling

Chemicals	Physical hazards											
	Explosives	Flammable	Aerosols	Oxidizing	Gases under pressure	Self-reactive	Pyrophoric liquids, solids	Self-heating	Emits flammable gas	Organic peroxides	Corrosivity	Desensitized explosives
BPA	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
BPAP	NC	NC	NC	NC	NC	MISS	MISS	MISS	NC	MISS	MISS	NC

Isosorbide	NC	NC	MISS	NC	MISS	MISS	MISS	NC	MISS	MISS	MISS	NC
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Table 17: Color coding explanation

XXX	Classified XXX according to CLP criteria, identified as SVHC
NC	Not classified according to CLP criteria
MISS	Data Missing
NP	Not identified as SVHC

4.1.6 SSbD Score – Step 1

Based on the previous results, an SSbD Score for Step 1 was derived for each substance despite the data gaps. BPA and BPAP don't pass Criterion H1 in both innovation stages. The scoring for Isosorbide was based on the available data, given the presence of data gaps in both stages, particularly in relation to physical hazards. The scoring system followed in this Step is based on the one suggested in the JRC SSbD report (Caldeira et al., 2022).

Table 18: SSbD Score Step 1 – Early Innovation

Chemical	SSbD Score Step 1	Comment	The scoring is based on the SSbD criteria and evaluation system for Step 1
BPA	0	BPA doesn't pass Criterion H1 because it is predicted to be a respiratory sensitizer	Level 0 – chemicals that do not pass hazard criterion H1 (most harmful substances)
BPAP	0	BPAP doesn't pass Criterion H1 because it is predicted to be a respiratory sensitizer	Level 1 – chemicals that pass hazard criterion H1 but do not pass criterion H2
Isosorbide	INC	A score cannot be derived for isosorbide because there are inconclusive results in the prediction of respiratory sensitization	Level 2– chemicals that pass hazard criteria H1 and H2 but do not pass criterion H3 Level 3 – chemicals that pass all safety criteria in Step 1

Table 19: SSbD Score Step 1 – Late Innovation after data gap filling

Chemical	SSbD Score Step 1	Comment	The scoring is based on the SSbD criteria and evaluation system for Step 1
BPA	0	BPA doesn't pass Criterion H1 because it is classified as an endocrine disruptor for HH and ENV and toxic to reproduction	Level 0 – chemicals that do not pass hazard criterion H1 (most harmful substances)
BPAP	0	BPAP doesn't pass Criterion H1 because it has been assessed to be an endocrine disruptor for HH	Level 1 – chemicals that pass hazard criterion H1 but do not pass criterion H2 Level 2– chemicals that pass hazard criteria H1 and H2 but do not pass criterion H3
Isosorbide	3	Isosorbide passes the safety criteria in Step 1 based on the available data	Level 3 – chemicals that pass all safety criteria in Step 1

4.2 Step 2 - Human health and safety aspects in the chemical/material production and processing phase

4.2.1 Occupational exposure - Approach

In Step 2, ECETOC TRA was chosen to be applied for the occupational exposure and risk assessment in both innovation stages. ECETOC TRA is a tier 1 exposure model for estimating the risk of exposure to chemicals, which is easy-to-use and includes a user-friendly interface. It consists of three main components; workers, consumers, and the environment, where for each of them there is a separate exposure estimation model. In this case, the component of worker exposure was employed to calculate the exposure via inhalation and by dermal route. The general physicochemical properties of the substance (molecular weight, vapor pressure), as well as information regarding the chemical production (process categories - PROCs) and the respective operational conditions (OCs), must be defined. Additionally, despite the lack of data on physical hazards (Step 1), the assessment was continued for the purpose of this case study.

In late innovation the PROCs and the physical state of each substance were found in the ECHA database. The PROCs were defined based on the REACH dossier of BPA. For the production stage of the polycarbonate bottle, in particular, we used the corresponding use map for plastic article production found in the ECHA use maps library¹⁶ (EuPC). A more conservative approach was applied in early innovation by considering one general PROC for each contributing scenario, based on the data limitation. The PROCs were defined based on the use description guidance provided by ECHA (ECHA, 2015). PROCs involving open processes, such as PROC 4 for manufacture, as well as activities where exposure may occur, were selected to capture a worst-case scenario approach. This selection was made while ensuring that each PROC is relevant to the contributing scenario. Another approach that could be followed in early innovation, is the assumption that the PROCs can be defined based on similar existing processes.

In order to perform a comparative assessment of the three substances under study, the same OCs and Risk Mitigation Measures (RMMs) were employed (Table 105– Appendix). Given the constraints of available data and considering a worst-case scenario, basic RMMs that are not based on personal protective equipment (PPE) were taken into account. Therefore, a full 8hr shift was chosen as the duration of each activity, while the room ventilation was considered 'good' with no Local Exhaust Ventilation (LEV). Regarding PPE, workers were considered to wear protective gloves with 80% effectiveness (the lowest effectiveness that TRA provides), while no use of respiratory protection was assumed. Regarding the physical state and dustiness level of each substance, they were defined using similar substances and BPA as a reference. Thus, in most contributing scenarios, the substances were solid with low dustiness (polycarbonate application), whereas in case of epoxy resin application the substances were liquids. In addition, the concentration of the substance in the manufacture and polycarbonate/epoxy resin production was considered the highest (>25%), whereas the concentration in the PC bottles/epoxy paint was considered very low (<1%) to account for the probability of monomer residues. Finally, the type of setting was industrial, as the uses assessed were industrial.

In early innovation, the required physicochemical properties (molecular weight, vapor pressure) were predicted based on the chemical structure using the VEGA model. Regarding the derivation of the respective reference values (DNELs), the approach described in the section 3.4 was followed. More specifically, in early innovation, the VEGA model was used to predict a NOAEL value based on a training set of repeated dose (90 days) oral toxicity in rats experimental protocol¹⁷. A long-term DNEL for workers has been derived for both inhalation and dermal exposure of each substance. The VEGA NOAEL value was used as a dose descriptor and converted to a DNEL value using default assessment factors

¹⁶ <https://echa.europa.eu/el/csr-es-roadmap/use-maps/use-maps-library>

¹⁷ https://www.vegahub.eu/vegahub-dwn/qmrf/QMRF_NOAEL_IRFMN.pdf

recommended by ECHA based on the experimental protocol. As the NOAEL was derived from QSARs, an additional assessment factor on the quality of the whole database was applied to account for the potential uncertainties (ECHA, 2011). Since there is no indication of the assessment factor range that should be used for quality of data, an assessment factor of 3 (default is 1) was assumed based on the higher uncertainty occurring from the use of QSAR predictions. However, it should be noted that the reliability of the VEGA predictions was not further evaluated (low reliability). Therefore, the results' accuracy is limited and uncertainty high. Further testing (such as read-across, in-vitro testing) and validation is required to move forward across the innovation process. The corresponding values are presented in Table 103 of the Appendix.

In late innovation, all the required physicochemical properties were retrieved from the ECHA and the US CompTox databases. Regarding the reference values, the long-term DNELs for BPA and Isosorbide (only for dermal route) were obtained from the REACH Registration Dossier of each substance. No DNEL for inhalation route was available in the dossier of Isosorbide. To fill this data gap, a NOAEL value from a repeated dose toxicity oral study in rats registered in the REACH dossier of Isosorbide was used. As previously mentioned (section 3.4), the availability of toxicological data for BPAP in late innovation is quite limited. Moreover, there are no registered toxicological thresholds for BPAP, as well as a limited number of toxicological studies. Therefore, the same toxicological thresholds were used for both innovation stages. Nevertheless, it should be highlighted that this approach was followed to fill the data gaps of the current case study and proceed with the assessment. Additionally, it is an indication of the potential challenges that may arise during the evaluation process of an existing substance with limited data.

Table 20: DNEL values used for the assessment

Reference value	BPA DNELs		BPAP DNELs		Isosorbide DNELs	
	Early Innovation	Late Innovation	Early Innovation	Late Innovation	Early Innovation	Late Innovation
<i>Worker Inhalation (mg/m³)</i>	0.138	2	0.19		12.88	165.23
<i>Worker Dermal (mg/kg bw day)</i>	0.039	0.066	0.055		3.65	697.29

In the following section (4.2.2), the worker exposure concentrations and the respective Risk Characterization Ratios (RCR) for the different contributing scenarios and exposure routes (inhalation and dermal) are presented.

4.2.2 ECETOC TRA

In the tables below, the occupational exposure results in early and late innovation for both applications (polycarbonate and epoxy resin applications) are presented. Each table represents a different contributing scenario based on the application and includes the exposure and RCR estimates. The RCR values that are greater than 1 are highlighted with red color.

4.2.2.1 Chemical manufacture

The following tables provide detailed estimates of the occupational exposure occurred during the manufacturing stage. This includes the assessment of exposure through both inhalation and dermal routes for each PROC. The estimates are further accompanied by the corresponding RCRs for both inhalation and dermal routes, as well as the RCR representing the combined total exposure.

4.2.2.1.1 *Early Innovation*

Table 21: ECETOC TRA results in the manufacturing stage

CSs	Chemical manufacture					
	BPA		BPAP		Isosorbide	
	Exposure	RCR	Exposure	RCR	Exposure	RCR
PROC 4						
Inhalation, long term (mg/m ³)	0.35	2.54	0.35	1.84	0.35	0.027
Dermal, long term (mg/kg/day)	1.371	35.15	1.371	24.94	1.371	0.376
Total exposure, long term		37.69		26.78		0.403

4.2.2.1.2 *Late Innovation*

Table 22: ECETOC TRA results in the manufacturing stage

CSs	Chemical manufacture					
	BPA		BPAP		Isosorbide	
	Exposure	RCR	Exposure	RCR	Exposure	RCR
PROC 2						
Inhalation, long term (mg/m ³)	0.007	0.0035	0.007	0.04	0.07	4.2E-04
Dermal, long term (mg/kg/day)	0.274	4.156	0.274	4.99	0.137	2.0E-04
Total exposure, long term		4.159		5.02		6.2E-04
PROC 8b						
Inhalation, long term (mg/m ³)	0.07	0.035	0.07	0.37	0.07	4.2E-04
Dermal, long term (mg/kg/day)	2.743	41.56	2.742	49.87	2.742	3.9E-03
Total exposure, long term		41.59		50.24		4.4E-03
PROC 9						
Inhalation, long term (mg/m ³)	0.07	0.035	0.07	0.37	0.35	2.1E-03
Dermal, long term (mg/kg/day)	1.371	20.78	1.371	24.94	1.371	2.0E-03
Total exposure, long term		20.81		25.30		4.1E-03

4.2.2.2 Polycarbonate application

The following tables provide detailed estimates of the occupational exposure occurred during the polycarbonate and bottle production, respectively. This includes the assessment of exposure through both inhalation and dermal routes for each PROC. The estimates are further accompanied by the corresponding RCRs for both inhalation and dermal routes, as well as the RCR representing the combined total exposure.

4.2.2.2.1 *Early Innovation*

Table 23: ECETOC TRA results in the polycarbonate production

CSs	Chemical manufacture					
	BPA		BPAP		Isosorbide	
	Exposure	RCR	Exposure	RCR	Exposure	RCR
PROC 4						
Inhalation, long term (mg/m ³)	0.35	2.54	0.35	1.84	0.35	0.027
Dermal, long term (mg/kg/day)	1.371	35.15	1.371	24.94	1.371	0.376
Total exposure, long term		37.69		26.78		0.403

Table 24: ECETOC TRA results in the PC bottle production

CSs	PC bottle production					
	BPA		BPAP		Isosorbide	
	Exposure	RCR	Exposure	RCR	Exposure	RCR
PROC 14						
Inhalation, long term (mg/m ³)	7.00E-03	0.05	7.00E-03	0.0386	7.00E-03	5.43E-04
Dermal, long term (mg/kg/day)	6.86E-02	1.76	6.86E-02	1.25	6.86E-02	0.0188
Total exposure, long term		1.81		1.29		0.19

4.2.2.2.2 *Late Innovation*

Table 25: ECETOC TRA results in the polycarbonate production

Polycarbonate Production						
CSs	BPA		BPAP		Isosorbide	
	Exposure	RCR	Exposure	RCR	Exposure	RCR
PROC 1						
Inhalation, long term (mg/m ³)	0.007	0.0035	0.007	0.04	0.007	4.24E-05
Dermal, long term (mg/kg/day)	0.007	0.104	0.007	0.12	0.007	9.83E-06
Total exposure, long term		0.107		0.16		5.2E-05
PROC 2						
Inhalation, long term (mg/m ³)	0.007	0.0035	0.007	0.04	0.007	4.24E-05
Dermal, long term (mg/kg/day)	0.274	4.156	0.274	4.99	0.274	3.93E-04
Total exposure, long term		4.159		5.02		4.36E-04
PROC 8b						
Inhalation, long term (mg/m ³)	0.07	0.035	0.07	0.37	0.07	4.24E-04
Dermal, long term (mg/kg/day)	2.743	41.56	2.742	49.87	2.742	3.93E-03
Total exposure, long term		41.59		50.24		4.36E-03

Table 26: ECETOC TRA results in the PC bottle production

PC bottle production						
CSs	BPA		BPAP		Isosorbide	
	Exposure	RCR	Exposure	RCR	Exposure	RCR
PROC 9						
Inhalation, long term (mg/m ³)	0.007	3.5E-03	0.007	0.037	0.007	4.24E-05
Dermal, long term (mg/kg/day)	0.137	2.08	0.137	2.49	0.137	1.97E-04
Total exposure, long term		2.08		2.53		2.39E-04
PROC 8b						
Inhalation, long term (mg/m ³)	0.007	3.5E-03	0.007	0.037	0.007	4.24E-05
Dermal, long term (mg/kg/day)	0.274	4.15	0.274	4.99	0.274	3.93E-04
Total exposure, long term		4.15		5.03		4.35E-04
PROC 14						
Inhalation, long term (mg/m ³)	0.007	3.5E-03	0.007	0.037	0.007	4.24E-05
Dermal, long term (mg/kg/day)	0.069	1.04	0.069	1.25	0.069	9.84E-05
Total exposure, long term		1.04		1.29		1.41E-04
PROC 6						
Inhalation, long term (mg/m ³)	0.007	3.5E-03	0.007	0.037	0.007	4.24E-05
Dermal, long term (mg/kg/day)	0.549	8.31	0.549	9.97	0.549	7.87E-04
Total exposure, long term		8.31		10.00		8.29E-04
PROC 10						
Inhalation, long term (mg/m ³)	0.035	0.0175	0.035	0.184	0.035	2.12E-04
Dermal, long term (mg/kg/day)	0.549	8.31	0.549	9.97	0.549	7.86E-04
Total exposure, long term		8.33		10.15		9.98E-04
PROC 15						
Inhalation, long term (mg/m ³)	0.007	3.5E-03	0.007	0.037	0.007	4.24E-05
Dermal, long term (mg/kg/day)	6.80E-03	0.10	6.80E-03	0.125	6.80E-03	9.75E-06
Total exposure, long term		0.10		0.162		5.21E-05

4.2.2.3 Epoxy resin application

The following tables provide detailed estimates of the occupational exposure occurred during the epoxy resin and paint production, respectively. This includes the assessment of exposure through both inhalation and dermal routes for each PROC. The estimates are further accompanied by the corresponding RCRs for both inhalation and dermal routes, as well as the RCR representing the combined total exposure.

4.2.2.3.1 Early Innovation

Table 27: ECETOC TRA results in the epoxy resin application

Epoxy resin Production

CSs	BPA		BPAP		Isosorbide	
	Exposure	RCR	Exposure	RCR	Exposure	RCR
PROC 4						
Inhalation, long term (mg/m ³)	0.35	2.54	0.35	1.84	0.35	0.027
Dermal, long term (mg/kg/day)	1.371	35.15	1.371	24.94	1.371	0.376
Total exposure, long term		37.69		26.78		0.403

Table 28: ECETOC TRA results in the epoxy paint application

Epoxy paint Production						
CSs	BPA		BPAP		Isosorbide	
	Exposure	RCR	Exposure	RCR	Exposure	RCR
PROC 5						
Inhalation, long term (mg/m ³)	0.067	0.48	0.085	0.46	0.043	3.3E-03
Dermal, long term (mg/kg/day)	0.274	7.03	0.274	4.99	0.274	7.5E-02
Total exposure, long term		7.52		10.92		7.8E-02

4.2.2.3.2 Late Innovation

Table 29: ECETOC TRA results in the epoxy resin application

Epoxy resin Production						
CSs	BPA		BPAP		Isosorbide	
	Exposure	RCR	Exposure	RCR	Exposure	RCR
PROC 1						
Inhalation, long term (mg/m ³)	0.007	0.0035	0.007	0.04	0.007	4.24E-05
Dermal, long term (mg/kg/day)	0.007	0.104	0.007	0.12	0.007	9.83E-06
Total exposure, long term		0.107		0.16		4.09E-03
PROC 2						
Inhalation, long term (mg/m ³)	0.007	0.0035	0.007	0.04	0.007	4.24E-05
Dermal, long term (mg/kg/day)	0.274	4.156	0.274	4.99	0.274	3.93E-04
Total exposure, long term		4.159		5.02		6.20E-04
PROC 3						
Inhalation, long term (mg/m ³)	0.07	0.035	0.07	0.37	0.07	4.24E-04
Dermal, long term (mg/kg/day)	0.137	2.078	0.137	2.49	0.137	1.97E-04
Total exposure, long term		2.113		2.86		4.36E-03
PROC 4						
Inhalation, long term (mg/m ³)	0.35	0.175	0.35	1.84	0.35	2.12E-03
Dermal, long term (mg/kg/day)	1.371	20.78	1.371	24.94	1.371	1.97E-03
Total exposure, long term		20.95		26.78		5.22E-05
PROC 5						
Inhalation, long term (mg/m ³)	0.35	0.175	0.35	1.84	0.35	2.12E-03
Dermal, long term (mg/kg/day)	2.743	41.56	2.743	49.87	2.743	3.93E-03
Total exposure, long term		41.73		51.71		4.36E-04
PROC 8b						
Inhalation, long term (mg/m ³)	0.07	0.035	0.07	0.37	0.07	4.24E-04
Dermal, long term (mg/kg/day)	2.743	41.56	2.743	49.87	2.743	3.93E-03
Total exposure, long term		41.59		50.24		6.20E-04
PROC 8b						
Inhalation, long term (mg/m ³)	0.133	0.067	0.169	0.89	0.085	5.16E-04
Dermal, long term (mg/kg/day)	0.549	8.311	0.549	9.97	0.549	7.87E-04
Total exposure, long term		8.378		10.86		4.09E-03
PROC 8b						
Inhalation, long term (mg/m ³)	0.067	0.033	0.085	0.45	0.043	2.58E-04
Dermal, long term (mg/kg/day)	0.274	4.156	0.274	4.99	0.274	3.93E-04
Total exposure, long term		4.189		5.43		6.05E-03
PROC 5						
Inhalation, long term (mg/m ³)	0.067	0.033	0.085	1.55	0.043	2.58E-04
Dermal, long term (mg/kg/day)	0.274	4.156	0.274	4.99	0.274	3.93E-04
Total exposure, long term		4.189		6.53		4.36E-03

Table 30: ECETOC TRA results in the epoxy paint application

Epoxy paint Production						
CSs	BPA		BPAP		Isosorbide	
	Exposure	RCR	Exposure	RCR	Exposure	RCR

PROC 1						
Inhalation, long term (mg/m ³)	0.007	0.003	0.008	0.04	0.004	2.6E-05
Dermal, long term (mg/kg/day)	0.001	0.010	0.001	0.014	0.001	9.8E-07
Total exposure, long term		0.014		0.06		2.7E-05
PROC 2						
Inhalation, long term (mg/m ³)	0.067	0.033	0.085	0.45	0.043	2.6E-04
Dermal, long term (mg/kg/day)	0.027	0.416	0.027	0.55	0.027	3.9E-05
Total exposure, long term		0.449		0.99		3.0E-04
PROC 3						
Inhalation, long term (mg/m ³)	0.067	0.033	0.085	0.45	0.043	2.6E-04
Dermal, long term (mg/kg/day)	0.014	0.208	0.014	0.27	0.014	2.0E-05
Total exposure, long term		0.241		0.72		2.8E-04
PROC 4						
Inhalation, long term (mg/m ³)	0.067	0.033	0.085	0.45	0.043	2.6E-04
Dermal, long term (mg/kg/day)	0.137	2.078	0.137	2.74	0.137	2.0E-04
Total exposure, long term		2.111		3.19		4.5E-04
PROC 5						
Inhalation, long term (mg/m ³)	0.067	0.033	0.085	0.45	0.043	2.6E-04
Dermal, long term (mg/kg/day)	0.274	4.156	0.274	5.49	0.274	3.9E-04
Total exposure, long term		4.189		5.93		6.5E-04
PROC 7						
Inhalation, long term (mg/m ³)	66.582	33.29	84.69	445.73	42.62	2.6E-01
Dermal, long term (mg/kg/day)	0.857	12.99	0.857	17.14	0.857	1.2E-03
Total exposure, long term		46.28		462.87		2.6E-01
PROC 8a						
Inhalation, long term (mg/m ³)	0.067	0.033	0.085	0.45	0.043	2.6E-04
Dermal, long term (mg/kg/day)	0.549	8.31	0.549	10.97	0.549	7.9E-04
Total exposure, long term		8.34		11.42		1.0E-03
PROC 8b						
Inhalation, long term (mg/m ³)	0.067	0.033	0.085	0.45	0.043	2.6E-04
Dermal, long term (mg/kg/day)	0.274	4.16	0.274	5.49	0.274	3.9E-04
Total exposure, long term		4.19		5.93		6.5E-04
PROC 9						
Inhalation, long term (mg/m ³)	0.067	0.033	0.085	0.45	0.043	2.6E-04
Dermal, long term (mg/kg/day)	0.274	2.08	0.137	2.74	0.137	2.0E-04
Total exposure, long term		2.11		3.19		4.5E-04
PROC 10						
Inhalation, long term (mg/m ³)	6.658	3.33	8.469	44.57	4.262	2.6E-02
Dermal, long term (mg/kg/day)	0.549	8.31	0.549	10.97	0.549	7.9E-04
Total exposure, long term		11.64		55.54		2.7E-02
PROC 13						
Inhalation, long term (mg/m ³)	0.067	0.033	0.085	0.45	0.043	2.6E-04
Dermal, long term (mg/kg/day)	0.274	4.156	0.274	5.49	0.274	3.9E-04
Total exposure, long term		4.19		5.93		6.5E-04

4.2.2.4 Discussion

Based on the ECETOC TRA results, it is observed that many of the inhalation and dermal exposure estimates for the substances under assessment are identical. This occurred when the three substances were in solid physical form and had the same level of dustiness (e.g., manufacturing or PC bottle production stages). The ECETOC TRA takes into account the dustiness of the substance and groups it into a respective band. In cases where the substances were in liquid form (e.g. epoxy paint production), the inhalation exposure was determined by the vapor pressure of the substance, while the dermal exposure estimates are still identical in each contributing scenario. This occurrence was also observed after comparing the exposure estimates between the two innovation stages. Therefore, if the exposure estimates are identical, the RCRs are only determined by the magnitude of the toxicological thresholds (DNELs). In general, ECETOC TRA is a tier 1 model that provides a conservative and basic exposure assessment. A higher tier and mechanistic exposure model, such as ART¹⁸, could be employed in late innovation, providing exposure estimates with lower uncertainty. Furthermore, a more conservative approach could be applied in early innovation by considering one general PROC for each contributing

¹⁸ <https://www.advancedreachtool.com/>

scenario, based on the data limitation. However, it could eliminate the exploration of scenarios and testing of potential risks that may arise in the manufacturing and processing of a chemical/material. In general, occupational exposure in early innovation could be addressed by exploring scenarios with different PROCs and OCs.

4.2.3 Environmental exposure – Approach

INTEGRA was employed for the environmental exposure and risk assessment in both steps 2 and 3. INTEGRA is a computational platform that integrates environmental fate, exposure, and internal dose. It consists of four modelling modules. The user can run only the module that is interested in. In the current case study, one of the INTEGRA models used was the multimedia environmental model. The multimedia environmental modelling framework for INTEGRA, follows the ECHA guidance on information requirements and chemical safety assessment. All different spatial scales (local, regional, continental and global), media exchange (air, soil, water, sediment and transfer to food items such as crops, meat, milk and fish) and environmental processes (emissions, advection, diffusion, and degradation) are taken into account.

In order to run INTEGRA, the user needs to specify the production volume of the chemical and the respective ERC for each contributing scenario. The production volume for BPAP and isosorbide cannot be equal to that of BPA when all amounts are expressed in kilograms or tons, due to the fact that the three molecules have different molecular weights. Consequently, equal masses correspond to different mole ratios, resulting in an improper assessment of product structural proportions. To ensure an optimal transition from BPA to alternatives, the corresponding tonnage was converted to moles produced per year. The aim was to equalize the mole amounts for all compounds. Taking into account the molecular weight of each chemical, we calculated the expected production volume of both BPAP and isosorbide. The production volumes that were applied to INTEGRA are presented in the table below (Table 31) (Fischer et al., 2014). The ERCs were set according to the REACH registration dossier of BPA and the respective ECHA guidance on use descriptors (ECHA, 2015), applying the default release factors for each use. In relation to other required information, such as physicochemical and environmental fate properties, the same approach as in Step 2 was followed. In early innovation, VEGA and EPISuite QSAR models were employed to predict physicochemical (e.g. vapor pressure, partition coefficient) and environmental fate properties (e.g. degradation constant rates), respectively. In late innovation, this information was sourced from the ECHA and US CompTox databases. In situations where there was still missing information, such as for BPAP, QSAR models were utilized to fill in these gaps. All this information is presented in

Table 101 and Table 102 of the Appendix.

Table 31: Production volumes used for each contributing scenario

Contributing scenario	Production volume (tn/yr)		
	BPA	BPAP	Isosorbide
<i>Manufacturing</i>	1.15E+06	1.46E+06	7.46E+05
<i>Polycarbonate production</i>	8.65E+05	1.10E+06	5.61E+05
<i>Epoxy resins production</i>	1.92E+05	2.44E+05	9.35E+04
<i>Polycarbonate bottle production</i>	2.16E+04	2.75E+04	1.40E+04
<i>Epoxy paint production</i>	1.19E+05	1.51E+05	5.80E+04
<i>Polycarbonate bottle (consumer stage)</i>	2.16E+04	2.75E+04	1.40E+04
<i>Epoxy paint (consumer stage)</i>	1.19E+05	1.51E+05	5.80E+04

Based on the data in Table 31, the calculation of the environmental releases was performed. The environmental releases were identical for both innovation stages, since they only depend on the tonnage value and the corresponding ERC.

Table 32: Environmental release rates in Step 2

	<i>Media</i>	BPA	BPAP	Isosorbide	Units
ERC 1	<i>Water</i>	1.89E+05	2.43E+05	1.23E+05	kg/day
	<i>Air</i>	1.58E+05	2.00E+05	1.02E+05	kg/day
	<i>Soil</i>	315	400.7	204.4	kg/day
ERC 6c – polycarbonate production	<i>Water</i>	1.18E+05	1.51E+05	7.69E+04	kg/day
	<i>Air</i>	1.18E+05	1.51E+05	7.69E+04	kg/day
	<i>Soil</i>	0	0	0	kg/day
ERC 6a – epoxy resin production	<i>Water</i>	1.05E+04	1.33E+04	5.12E+03	kg/day
	<i>Air</i>	2.62E+04	3.33E+04	1.28E+04	kg/day
	<i>Soil</i>	5.25E+02	6.67E+02	2.56E+02	kg/day
ERC 5 – polycarbonate application	<i>Water</i>	2.96E+04	3.77E+04	1.92E+04	kg/day
	<i>Air</i>	2.96E+04	3.77E+04	1.92E+04	kg/day
	<i>Soil</i>	592.4	753.5	384.4	kg/day
ERC 5 – epoxy resin application	<i>Water</i>	1.63E+05	2.07E+05	7.94E+04	kg/day
	<i>Air</i>	1.63E+05	2.07E+05	7.94E+04	kg/day
	<i>Soil</i>	3.25E+03	4.14E+03	1.59E+03	kg/day
Total Releases - polycarbonate	<i>Water</i>	1.46E+08	1.88E+08	7.98E7	kg/year
	<i>Air</i>	1.40E+08	1.78E+08	7.24E7	kg/year
	<i>Soil</i>	4.46E+05	5.68E5	2.15E5	kg/year
Total Releases – epoxy resin	<i>Water</i>	1.32E+08	1.68E+08	7.50E+07	kg/year
	<i>Air</i>	1.26E+08	1.61E+08	7.05E+07	kg/year
	<i>Soil</i>	1.49E+06	1.90E+06	7.47E+05	kg/year

Regarding the ecotoxicological thresholds in the environmental risk assessment, a similar procedure was applied. In order to fill the data gaps in early innovation, ECOSAR QSAR model was employed to predict chronic aquatic toxicity. From these predictions, the lowest chronic toxicity value for freshwater aquatic species was divided by an assessment factor of 10 to derive the PNEC for freshwater. The PNEC for marine water was calculated by dividing by 10 the PNEC for freshwater. Moreover, the EPM method was applied to calculate the PNECs for sediment and soil (as shown in

Table 33).

Table 33: Predicted No Effect Concentrations (PNECs) using QSARs (early innovation)

PNECs	Freshwater (mg/l)	Marine water (mg/l)	Freshwater sediment (mg/kg dw)	Marine water sediment (mg/kg dw)	Soil (mg/kg dw)	Source

BPA	0.027	0.0027	0.6405	0.064	0.508	ECOSAR* and EPM**
BPAP	0.011	0.0011	2.12	0.213	61.99	ECOSAR* and EPM**
Isosorbide	75.47	7.5	59.49	5.95	9.22	ECOSAR* and EPM**

* ECOSAR used for PNEC freshwater and STP

**EPM used for PNEC sediment and soil

The PNECs in late innovation were retrieved from the REACH registration dossier of each substance. However, there was no available data for BPAP. Thus, the same toxicological thresholds were used for both innovation stages, as shown in table below (Table 34).

Table 34: Predicted No Effect Concentrations (PNECs) (late innovation)

PNECs	Freshwater (mg/l)	Marine water (mg/l)	Freshwater sediment (mg/kg dw)	Marine water sediment (mg/kg dw)	Soil (mg/kg dw)	Source
BPA	0.023	0.019	1.2	0.24	62.28	ECHA
BPAP	0.011	0.0011	2.12	0.213	61.99	ECOSAR* and EPM**
Isosorbide	0.107	0.0011	0.4	0.04	2.40E-12	ECHA

* ECOSAR used for PNEC freshwater and STP

**EPM used for PNEC sediment and soil

In the following section (4.2.4), the environmental exposure concentrations and the respective Risk Characterization Ratios (RCR) for the different contributing scenarios are presented.

4.2.4 INTEGRA

In the tables below, the environmental exposure results in early and late innovation for both applications (polycarbonate and epoxy resin applications) are presented. Each table represents a different contributing scenario based on the application and includes the exposure and RCR estimates. For the current case study, only the regional PECs were taken into consideration. The RCR values that are greater than 1 are highlighted with red color.

4.2.4.1 Polycarbonate application

4.2.4.1.1 *Early Innovation*

Table 35: Predicted Effect Concentrations (PECs) using QSARs

Regional PECs	Freshwater (µg/l)	Marine water (µg/l)	Freshwater sediment (µg/kg dw)	Marine water sediment (µg/kg dw)	Soil (µg/kg dw)
BPA	1.36E+02	4.33E+01	2.07E+00	0.00E+00	5.31E+01
BPAP	1.54E+02	5.41E+01	2.32E+00	0.00E+00	5.07E+01
Isosorbide	4.24E-11	1.91E-09	3.61E-21	0.00E+00	5.15E-14

Table 36: Risk Characterization Ratios (RCRs) using QSARs

RCRs	Freshwater	Marine water	Freshwater sediment	Marine water sediment	Soil
BPA	5.91E+00	1.88E+01	3.23E-03	0.00E+00	1.04E-01
BPAP	1.40E+01	4.92E+01	1.09E-03	0.00E+00	2.95E-02
Isosorbide	5.62E-16	2.55E-13	6.06E-26	0.00E+00	5.59E-18

4.2.4.1.2 *Late Innovation*

Table 37: Predicted Effect Concentrations (PECs)

Regional PECs	Freshwater (µg/l)	Marine water (µg/l)	Freshwater sediment (µg/kg dw)	Marine water sediment (µg/kg dw)	Soil (µg/kg dw)
BPA	1.38E+02	4.34E+01	2.10E+00	0.00E+00	5.51E+01
BPAP	1.69E+02	5.47E+01	2.58E+00	0.00E+00	6.37E+01
Isosorbide	1.31E-11	7.71E-12	4.24E-11	1.917E-09	3.60E-21

Table 38: Risk Characterization Ratios (RCRs)

RCRs	Freshwater	Marine water	Freshwater sediment	Marine water sediment	Soil
BPA	5.98E+00	2.28E+00	1.75E-03	0.00E+00	1.49E-02
BPAP	1.54E+01	4.98E+01	1.21E-03	0.00E+00	3.71E-02
Isosorbide	1.23E-13	7.01E-13	1.06E-13	4.78E-11	2.25E-22

4.2.4.2 Epoxy resin application

4.2.4.2.1 *Early Innovation*

Table 39: Predicted Effect Concentrations (PECs) using QSARs

Regional PECs	Freshwater (µg/l)	Marine water (µg/l)	Freshwater sediment (µg/kg dw)	Marine water sediment (µg/kg dw)	Soil (µg/kg dw)
BPA	1.77E+02	5.66E+01	2.71E+00	0.00E+00	6.93E+01
BPAP	2.01E+02	7.10E+01	3.04E+00	0.00E+00	6.61E+01
Isosorbide	4.35E-11	1.96E-09	3.27E-21	0.00E+00	4.56E-14

Table 40: Risk Characterization Ratios (RCRs) using QSARs

RCRs	Freshwater	Marine water	Freshwater sediment	Marine water sediment	Soil
BPA	7.72E+00	2.46E+01	4.22E-03	0.00E+00	1.36E-01
BPAP	1.83E+01	6.46E+01	1.43E-03	0.00E+00	3.85E-02
Isosorbide	5.76E-16	2.61E-13	5.49E-26	0.00E+00	4.94E-18

4.2.4.2.2 *Late Innovation*

Table 41: Predicted Effect Concentrations (PECs)

Regional PECs	Freshwater (µg/l)	Marine water (µg/l)	Freshwater sediment (µg/kg dw)	Marine water sediment (µg/kg dw)	Soil (µg/kg dw)
BPA	1.80E+02	5.67E+01	2.74E+00	0.00E+00	7.19E+01
BPAP	2.22E+02	7.18E+01	3.37E+00	0.00E+00	8.29E+01
Isosorbide	1.31E-11	7.70E-12	4.35E-11	1.96E-09	3.27E-21

Table 42: Risk Characterization Ratios (RCRs)

RCRs	Freshwater	Marine water	Freshwater sediment	Marine water sediment	Soil
BPA	7.82E+00	2.98E+00	2.28E-03	0.00E+00	1.94E-02
BPAP	2.01E+01	6.53E+01	1.59E-03	0.00E+00	4.83E-02
Isosorbide	1.23E-13	7.00E-13	1.09E-13	4.90E-11	2.04E-22

4.2.4.3 Discussion

Upon comparing the results from the two stages, no significant differences in PECs and RCRs were found. The reason for this occurrence can be attributed to the utilization of estimated environmental releases and degradation rates in both cases, rather than measured ones in late innovation. Given that, the values of RCRs depend mainly on the corresponding PNECs. In the case of BPAP, the same PNECs were applied. The main differences are present in the PNECs of Isosorbide, where the predicted values are much higher than the measured ones. Considering the low values of the calculated RCRs in both innovation stages, the impact of this variation is not significant. In conclusion, the relevance and the quality of the input data can significantly influence the expected results.

4.2.5 SSbD Score – Step 2

The scoring system followed in this step (Table 43) is based on the one suggested in the JRC SSbD case study (Caldeira et al., 2023). The PROCs and ERCs of each contributing scenario were taken into account for the derivation of the SSbD score in Step 2.

Table 43: Scoring System for Step 2

For each CS: PROC and ERC	
If total RCR<1	3
If total RCR>1 but all individual RCRs<1	2
If total RCR>1 but at least 1 individual RCRs>1	1
If total RCR>1 and more than one individual RCRs>1	0

4.2.5.1 Chemical manufacture

Table 44: SSbD Score Step 2 in the manufacture stage– Early Innovation

Chemical Manufacture		
Human Health		Environment
CSs	PROC 4	ERC 1
BPA	0	0
BPAP	0	0
Isosorbide	3	3

Table 45: SSbD Score Step 2 in the manufacture stage – Late Innovation

Chemical Manufacture					
Human Health					Environment
CSs	PROC 2	PROC 8b	PROC 9	SSbD Score	ERC 1
BPA	1	1	1	1	0
BPAP	1	1	1	1	0
CSs	PROC 4	PROC 3	PROC 8b	SSbD Score	ERC 1
Isosorbide	3	3	3	3	3

Based on the previous tables, it is observed that the SSbD scores are identical in both stages. This occurrence may depend on the respective PROCs and OCs used. Furthermore, although early and late innovations have different RCR values, they both result in the same SSbD score. The final result of exposure estimates and relevant RCRs may be influenced by the type of tool or data employed for their calculation. Therefore, it is important to consider the selection of the appropriate tool to ensure that the results obtained are reliable and accurate. Finally, it is essential for the assessor to also consider the detailed results of each stage.

4.2.5.2 Polycarbonate application

4.2.5.2.1 Early Innovation

Table 46: SSbD Score Step 2 for the polycarbonate application in the production of polycarbonate – Early Innovation

Polycarbonate Production		
Human Health		Environment
CSs	PROC 4	ERC 6c
BPA	0	0
BPAP	0	0
Isosorbide	3	3

Table 47: SSbD Score Step 2 for the polycarbonate application in the production of bottles – Early Innovation

PC bottle production		
Human Health		Environment
CSs	PROC 14	ERC 5
BPA	1	0
BPAP	1	0
Isosorbide	3	3

4.2.5.2.2 Late Innovation

Table 48: SSbD Score Step 2 in the production of polycarbonate – Late Innovation

Polycarbonate Production					
Human Health					Environment
CSs	PROC 1	PROC 2	PROC 8b	SSbD Score	ERC 6c
BPA	3	1	1	2	1
BPAP	3	1	1	2	0
Isosorbide	3	3	3	3	3

Table 49: SSbD Score Step 2 for the polycarbonate application in the production of bottles – Late Innovation

Production of PC Bottles								
Human Health								Environment
CSs	PROC 6	PROC 8b	PROC 9	PROC 10	PROC 14	PROC 15	SSbD Score	ERC 5
BPA	1	1	1	1	1	3	1	1
BPAP	1	1	1	1	1	3	1	0
Isosorbide	3	3	3	3	3	3	3	3

4.2.5.3 Epoxy resin application

4.2.5.3.1 Early innovation

Table 50: SSbD Score Step 2 for the epoxy resin application in the production of epoxy resin – Early Innovation

Epoxy Resin Production		
Human Health		Environment
CSs	PROC 4	ERC 6a
BPA	0	1
BPAP	0	0
Isosorbide	3	3

Table 51: SSbD Score Step 2 for the epoxy resin application in the production of epoxy paint – Early Innovation

Epoxy paint Production		
Human Health		Environment
CSs	PROC 5	ERC 5
BPA	1	0
BPAP	1	0
Isosorbide	3	3

4.2.5.3.2 Late Innovation

Table 52: SSbD Score Step 2 for the epoxy resin application in the production of epoxy resin – Late Innovation

Epoxy resin Production											
Human Health											Environment
CSs	PROC 1	PROC 2	PROC 3	PROC 4	PROC 5	PROC 8a	PROC 8b	PROC 8b	PROC 5	SSbD Score	ERC 6a
BPA	3	1	1	1	1	1	1	1	1	1	1
BPAP	3	1	2	1	1	1	1	1	1	1	0
Isosorbide	3	3	3	3	3	3	3	3	3	3	3

Table 53: SSbD Score Step 2 for the epoxy resin application in the production of epoxy paint – Late Innovation

Epoxy paint production													
Human Health													Environment
CSs	PROC 1	PROC 2	PROC 3	PROC 4	PROC 5	PROC 7	PROC 8a	PROC 8b	PROC 9	PROC 10	PROC 13	SSbD Score	ERC 5
BPA	3	3	3	1	1	0	1	1	1	0	1	1	1
BPAP	3	2	3	1	1	0	1	1	1	0	1	1	0
Isosorbide	3	3	3	3	3	3	3	3	3	3	3	3	3

4.2.5.4 Discussion

Overall, it has been noticed that the majority of SSbD scores during the early stages are lower compared to those in the later stages. This discrepancy is indicative of higher predicted risks in the former stage, as well as the application of a worst-case scenario. The reason for the higher prediction is due to the application of corresponding toxicological thresholds (DNELs). As previously mentioned, additional assessment factors were applied to the DNELs calculated based on QSARs to consider the reliability of these values. Consequently, the predicted DNELs demonstrated a more stringent and conservative approach, resulting in lower values when compared to the corresponding DNELs retrieved from the REACH dossier. Regarding the SSbD scores arising from the environmental risk assessment, a similar variation is noted. The use of QSARs to predict the PNECs can have an impact on the overall outcome. Additionally, it is important to note that this approach was taken due to limited data during early innovation. Moving towards the innovation process, where the data availability is increased, the assessor will test and apply more reliable methods to provide accurate results.

4.3 Step 3 - Human health and environmental aspects in the final application phase

In Step 3, a combination of tools was used to provide the required results. First of all, similarly with Step 2, INTEGRA was employed for the environmental exposure and risk assessment. Regarding the consumer exposure assessment, the choice of tools was based on the specific use scenario. In more detail, for the application of the polycarbonate reusable bottles, Vermeer FCM and INTEGRA were applied to derive the food concentrations and then the daily mean intake and RCRs, respectively. In the context of the epoxy paint application, CEM and INTEGRA were used for predicting the emission rates and then calculating the exposure concentrations and RCRs, respectively. This workflow is also previously described in Figure 8.

The methodology adopted for predicting the physicochemical, environmental fate and toxicological properties in this step was consistent with that employed in Step 2. The VEGA and EPISUITE models were used to predict the required input properties in early innovation, while the ECHA and US CompTox databases sourced the calculations in late innovation.

4.3.1 INTEGRA

To calculate the PECs and RCRs occurring from the activities in Step 3, the production volumes presented in Table 54 were used. Moreover, to assess the relevant safety aspects, the ERCs 10a and 11a were added to the contributing scenarios for the consumer stage, depending on the article category of each application.

Table 54: Production volumes used in Step 3

Contributing scenario	Production volume (tn/yr)		
	BPA	BPAP	Isosorbide
<i>Polycarbonate bottle (consumer stage)</i>	2.16E+04	2.75E+04	1.40E+04
<i>Epoxy paint (consumer stage)</i>	1.19E+05	1.51E+05	5.80E+04

Based on the data in Table 54, the calculation of the environmental releases was performed. The environmental releases were identical for both innovation stages, since they only depend on the tonnage value and the corresponding ERC.

Table 55: Environmental release rates in Step 3

	Media	BPA	BPAP	Isosorbide	Units
ERC 10a	Water	189.5	241.1	123	kg/day
	Air	2.962	3.768	1.922	kg/day
	Soil	189.5	241.1	123	kg/day
ERC 11a	Water	2.962	3.768	1.922	kg/day
	Air	2.962	3.768	1.922	kg/day

	Soil	0	0	0	kg/day
Total releases - polycarbonate	Water	6.92E+05	8.80E+05	4.49E+05	kg/year
	Air	1.08E4	1.38E+04	7.02E+03	kg/year
	Soil	6.92E+05	8.8E5	4.49E+05	kg/year
ERC 10a	Water	1.04E+03	1.32E+03	508.4	kg/day
	Air	16.30	20.68	7.945	kg/day
	Soil	1.04E+03	1.32E+03	508.4	kg/day
ERC 11a	Water	16.30	20.68	7.945	kg/day
	Air	16.30	20.68	7.945	kg/day
	Soil	0	0	0	kg/day
Total releases - epoxy resin	Water	3.80E+06	4.83E+06	1.85E+06	kg/year
	Air	5.94E+06	7.55E+04	2.90E+04	kg/year
	Soil	3.80E+06	4.83E+06	1.85E+06	kg/year

The following sections present the results of the environmental safety assessment occurring from the Step 3 activities in early and late innovation. The RCRs were predicted using the same PNECs as those use in Step 2 (see

Table 33 and Table 34). For the current case study, only the regional PECs were taken into consideration. The RCR values that are greater than 1 are highlighted with red color.

4.3.1.1 Polycarbonate application

4.3.1.1.1 Early Innovation

Table 56: Predicted Effect Concentrations (PECs) using QSARs

Regional PECs	Freshwater (µg/l)	Marine water (µg/l)	Freshwater sediment (µg/kg dw)	Marine water sediment (µg/kg dw)	Soil (µg/kg dw)
BPA	9.67E-01	3.83E-01	1.47E-02	0.00E+00	3.55E-03
BPAP	1.18E+00	4.85E-01	1.77E-02	0.00E+00	2.96E-02
Isosorbide	2.47E-12	1.11E-10	1.33E-21	0.00E+00	3.19E-16

Table 57: Risk Characterization Ratios (RCRs) using QSARs

RCRs	Freshwater	Marine water	Freshwater sediment	Marine water sediment	Soil
BPA	4.20E-02	1.66E-01	2.30E-05	0.00E+00	6.99E-06
BPAP	1.07E-01	4.41E-01	8.35E-06	0.00E+00	1.72E-05
Isosorbide	3.27E-17	1.48E-14	2.24E-26	0.00E+00	3.46E-20

4.3.1.1.2 *Late Innovation*

Table 58: Predicted Effect Concentrations (PECs)

Regional PECs	Freshwater (µg/l)	Marine water (µg/l)	Freshwater sediment (µg/kg dw)	Marine water sediment (µg/kg dw)	Soil (µg/kg dw)
BPA	9.70E-01	3.83E-01	1.48E-02	0.00E+00	7.51E-03
BPAP	1.22E+00	4.87E-01	1.86E-02	0.00E+00	0.00E+00
Isosorbide	8.25E-14	4.84E-14	9.86E-12	4.44E-10	2.13E-20

Table 59: Risk Characterization Ratios (RCRs) using QSARs

RCRs	Freshwater	Marine water	Freshwater sediment	Marine water sediment	Soil
BPA	4.22E-02	2.02E-02	1.23E-05	0.00E+00	2.03E-06
BPAP	1.11E-01	4.42E-01	8.79E-06	0.00E+00	0.00E+00
Isosorbide	7.71E-16	4.40E-15	2.47E-14	1.11E-11	1.33E-21

4.3.1.1.3 *Steps 2 and 3 – Environmental Exposure comparison*

A comparison between the environmental results of Steps 2 and 3 was performed. As indicated in the tables below, the contribution of the regional PECs is significantly higher (nearly 100%) in Step 2 compared to Step 3. As a result, the PECs and RCRs resulted in Step 3 were not taken into account in the derivation of the SSbD scores. This occurrence applies to both applications under assessment.

Early Innovation

Table 60: Comparison of PECs in Steps 2 and 3

Regional PECs	Freshwater (mg/l)		Marine water (mg/l)		Freshwater sediment (mg/kg dw)		Marine sediment (mg/kg dw)		Soil (mg/kg dw)	
	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3
BPA	1.36E+02	9.67E-01	4.33E+01	3.83E-01	2.07E+00	1.47E-02	0.00E+00	0.00E+00	5.31E+01	6.99E-06
BPAP	1.54E+02	1.18E+00	5.41E+01	4.85E-01	2.32E+00	1.77E-02	0.00E+00	0.00E+00	5.07E+01	1.72E-05
Isosorbide	4.24E-11	2.47E-12	1.91E-09	1.11E-10	3.61E-21	1.33E-21	0.00E+00	0.00E+00	5.15E-14	3.46E-20

Table 61: Example of Step 2 contribution to the regional PECs

Regional PECs	Freshwater (mg/l)	Marine water (mg/l)	Freshwater sediment (mg/kg dw)	Marine sediment (mg/kg dw)	Soil (mg/kg dw)
	Contribution - Step 2	Contribution - Step 2	Contribution - Step 2	Contribution - Step 2	Contribution - Step 2
BPA	99.29%	99.12%	99.29%	0.00E+00	100.00%
BPAP	99.24%	99.11%	99.24%	0.00E+00	100.00%

Isosorbide	94.50%	94.51%	73.08%	0.00E+00	100.00%
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Table 62: Comparison of RCRs in Steps 2 and 3

RCRs	Freshwater		Marine water		Freshwater sediment		Marine sediment		Soil	
	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3
BPA	5.91E+00	4.20E-02	1.88E+01	1.66E-01	3.23E-03	2.30E-05	0.00E+00	0.00E+00	1.04E-01	6.99E-06
BPAP	1.40E+01	1.07E-01	4.92E+01	4.41E-01	1.09E-03	8.35E-06	0.00E+00	0.00E+00	2.95E-02	1.72E-05
Isosorbide	5.62E-16	3.27E-17	2.55E-13	1.48E-14	6.06E-26	2.24E-26	0.00E+00	0.00E+00	5.59E-18	3.46E-20

Late Innovation

Table 63: Comparison of PECs in Steps 2 and 3 of polycarbonate application

Regional PECs	Freshwater (mg/l)		Marine water (mg/l)		Freshwater sediment (mg/kg dw)		Marine sediment (mg/kg dw)		Soil (mg/kg dw)	
	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3
BPA	1.38E+02	9.70E-01	4.34E+01	3.83E-01	2.10E+00	1.48E-02	0.00E+00	0.00E+00	5.51E+01	7.51E-03
BPAP	1.69E+02	1.22E+00	5.47E+01	4.87E-01	2.58E+00	1.86E-02	0.00E+00	0.00E+00	6.37E+01	0.00E+00
Isosorbide	1.31E-11	8.25E-14	7.71E-12	4.84E-14	4.24E-11	9.86E-12	1.917E-09	4.44E-10	3.60E-21	2.13E-20

Table 64: Comparison of RCRs in Steps 2 and 3

RCRs	Freshwater		Marine water		Freshwater sediment		Marine sediment		Soil	
	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3
BPA	5.98E+00	4.22E-02	2.28E+00	2.02E-02	1.75E-03	1.23E-05	0.00E+00	0.00E+00	1.49E-02	2.03E-06
BPAP	1.54E+01	1.11E-01	4.98E+01	4.42E-01	1.21E-03	8.79E-06	0.00E+00	0.00E+00	3.71E-02	0.00E+00
Isosorbide	1.23E-13	7.71E-16	7.01E-13	4.40E-15	1.06E-13	2.47E-14	4.78E-11	1.11E-11	2.25E-22	1.33E-21

4.3.1.2 Epoxy resin application

4.3.1.2.1 Early Innovation

Table 65: Predicted Effect Concentrations (PECs) using QSARs

Regional PECs	Freshwater (µg/l)	Marine water (µg/l)	Freshwater sediment (µg/kg dw)	Marine water sediment (µg/kg dw)	Soil (µg/kg dw)
BPA	4.85E+00	2.00E+00	7.31E-02	0.00E+00	1.22E-01
BPAP	1.29E+01	5.36E-01	1.94E-01	0.00E+00	1.44E+00
Isosorbide	9.86E-12	4.44E-10	6.87E-21	0.00E+00	1.65E-15

Table 66: Risk Characterization Ratios (RCRs) using QSARs

RCRs	Freshwater	Marine water	Freshwater sediment	Marine water sediment	Soil
BPA	2.11E-01	8.70E-01	1.14E-04	0.00E+00	2.41E-04
BPAP	1.17E+00	4.88E-01	9.13E-05	0.00E+00	8.40E-04
Isosorbide	1.31E-16	5.92E-14	1.16E-25	0.00E+00	1.79E-19

4.3.1.2.2 *Late Innovation*

Table 67: Predicted Effect Concentrations (PECs)

Regional PECs	Freshwater (µg/l)	Marine water (µg/l)	Freshwater sediment (µg/kg dw)	Marine water sediment (µg/kg dw)	Soil (µg/kg dw)
BPA	6.15E+01	4.01E+00	9.37E-01	0.00E+00	7.19E+01
BPAP	5.05E+00	2.01E+00	7.70E-02	0.00E+00	0.00E+00
Isosorbide	5.47E-14	3.21E-14	9.86E-12	4.44E-10	6.87E-21

Table 68: Risk Characterization Ratios (RCRs) using QSARs

RCRs	Freshwater	Marine water	Freshwater sediment	Marine water sediment	Soil
BPA	2.67E+00	2.11E-01	7.81E-04	0.00E+00	1.94E-02
BPAP	4.59E-01	1.83E+00	3.63E-05	0.00E+00	0.00E+00
Isosorbide	5.11E-16	2.92E-15	2.47E-14	1.11E-11	4.29E-22

4.3.1.2.3 *Steps 2 and 3 – Environmental Exposure Comparison*

Early Innovation

Table 69: Comparison of PECs in Steps 2 and 3

Regional PECs	Freshwater (mg/l)		Marine water (mg/l)		Freshwater sediment (mg/kg dw)		Marine sediment (mg/kg dw)		Soil (mg/kg dw)	
	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3
BPA	1.77E+02	4.85E+00	5.66E+01	2.00E+00	2.71E+00	7.31E-02	0.00E+00	0.00E+00	6.93E+01	1.22E-01
BPAP	2.01E+02	1.29E+01	7.10E+01	5.36E-01	3.04E+00	1.94E-01	0.00E+00	0.00E+00	6.61E+01	1.44E+00
Isosorbide	4.35E-11	9.86E-12	1.96E-09	4.44E-10	3.27E-21	6.87E-21	0.00E+00	0.00E+00	4.56E-14	1.65E-15

Table 70: Comparison of RCRs in Steps 2 and 3

RCRs	Freshwater		Marine water		Freshwater sediment		Marine sediment		Soil	
	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3
BPA	7.72E+00	2.11E-01	2.46E+01	8.70E-01	4.22E-03	1.14E-04	0.00E+00	0.00E+00	1.36E-01	2.41E-04
BPAP	1.83E+01	1.17E+00	6.46E+01	4.88E-01	1.43E-03	9.13E-05	0.00E+00	0.00E+00	3.85E-02	8.40E-04
Isosorbide	5.76E-16	1.31E-16	2.61E-13	5.92E-14	5.49E-26	1.16E-25	0.00E+00	0.00E+00	4.94E-18	1.79E-19

Late Innovation

Table 71: Comparison of PECs in Steps 2 and 3 of epoxy resin application

Regional PECs	Freshwater (mg/l)		Marine water (mg/l)		Freshwater sediment (mg/kg dw)		Marine sediment (mg/kg dw)		Soil (mg/kg dw)	
	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3
BPA	1.80E+02	6.15E+01	5.67E+01	4.01E+00	2.74E+00	9.37E-01	0.00E+00	0.00E+00	7.19E+01	7.19E+01
BPAP	2.22E+02	5.05E+00	7.18E+01	2.01E+00	3.37E+00	7.70E-02	0.00E+00	0.00E+00	8.29E+01	0.00E+00
Isosorbide	1.31E-11	5.47E-14	7.70E-12	3.21E-14	4.35E-11	9.86E-12	1.96E-09	4.44E-10	3.27E-21	6.87E-21

Table 72: Comparison of RCRs in Steps 2 and 3

RCRs	Freshwater		Marine water		Freshwater sediment		Marine sediment		Soil	
	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3	Step 2	Step 3
BPA	7.82E+00	2.67E+00	2.98E+00	2.11E-01	2.28E-03	7.81E-04	0.00E+00	0.00E+00	1.94E-02	1.94E-02
BPAP	2.01E+01	4.59E-01	6.53E+01	1.83E+00	1.59E-03	3.63E-05	0.00E+00	0.00E+00	4.83E-02	0.00E+00
Isosorbide	1.23E-13	5.11E-16	7.00E-13	2.92E-15	1.09E-13	2.47E-14	4.90E-11	1.11E-11	2.04E-22	4.29E-22

4.3.2 Vermeer FCM – Polycarbonate application

The use case related to the polycarbonate application falls under the scope of food contact materials (FCM). For this reason, Vermeer FCM v3.4 was employed to predict the chemical concentration in food. Vermeer FCM is a software designed for migration modeling of chemicals from FCM. Its current version is included in the MERLIN-Expo software. To run the model, there are specific input requirements, such as the migration testing conditions and the parameters of the system geometry. These parameters are scenario specific and must be defined in order to perform the assessment. To establish those parameters, a literature search was carried out, and the details of the parameters are provided in the tables below. Regarding the parameters characterizing the diffusion in the FCM, the model provides two options, one

for calculating the coefficient using the model and the other for entering measured data. In both innovation stages, the option for calculating the coefficient was chosen.

Table 73: Migration testing conditions used for Vermeer FCM retrieved from (Kubwabo et al., 2009)

Migration testing conditions	
Time (hours)	Value (°C)
24	4
2.5	22
2	40
8	40
24	40
96	40
240	40

Vermeer FCM provides the possibility to run the VEGA model, which is built in the tool, for predicting the k_{ow} values of each chemical. This function was applied during the early innovation, while in late innovation the k_{ow} values from the REACH dossier were used.

Table 74: Parameters used for Vermeer FCM (Xu et al., 2011)

Parameters				
Contact area between FCM and Food	550			cm ²
Density of FCM	1.2			g/cm ³
Thickness of the FCM layer	0.1			cm
Volume of food contained in FCM packaging	1000			cm ³
Initial Concentration of the chemical in FCM	7.1			mg/kg
Molar mass of the migrating chemical	BPA	BPAP	Isosorbide	g/mol
	228.28	290.36	146.14	
Log_{kw} (VEGA)	3.32	4.26	-1.33	-
Log_{kw}(ECHA)	3.32	2.3	-1.39	-

The results of the model are presented in the following figure (Figure 9), including the chemical concentration per food item. The resulted concentrations for BPA and Isosorbide were identical for both innovation stages. This occurrence is linked to the input data provided. The only difference between the two stages is the k_{ow} value which affects the predicted concentration values. In the case of BPA and Isosorbide, the k_{ow} values there are no differences in these values. Only the food concentrations regarding BPAP showed differences, considering the k_{ow} value.

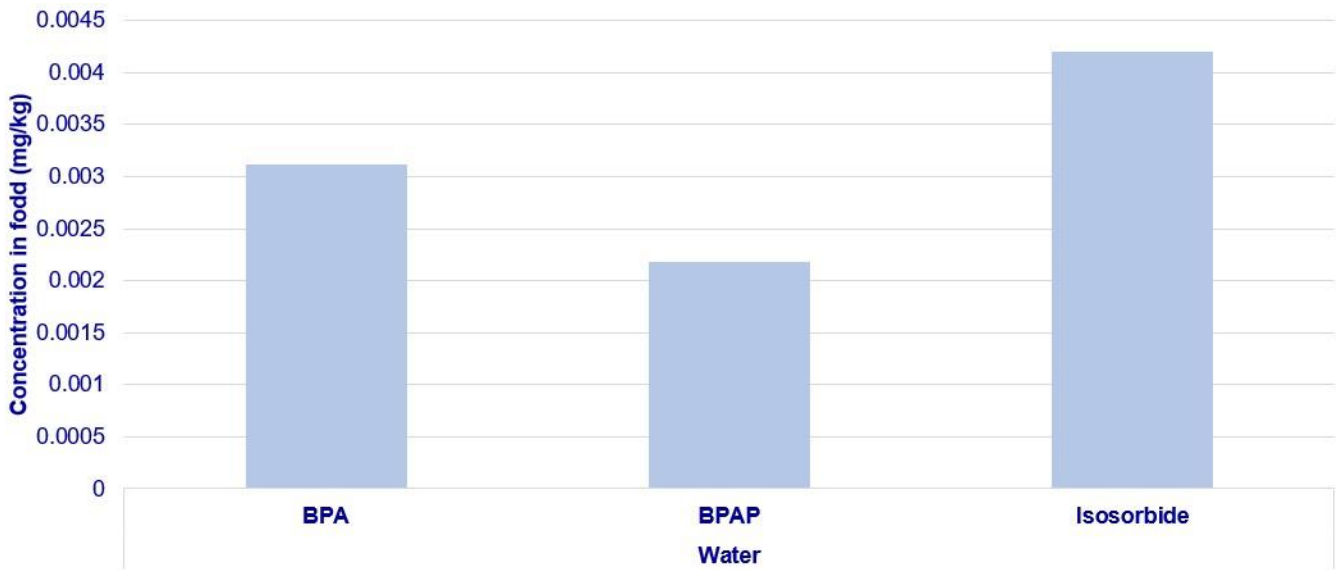


Figure 9: Vermeer FCM results per food item (early innovation)

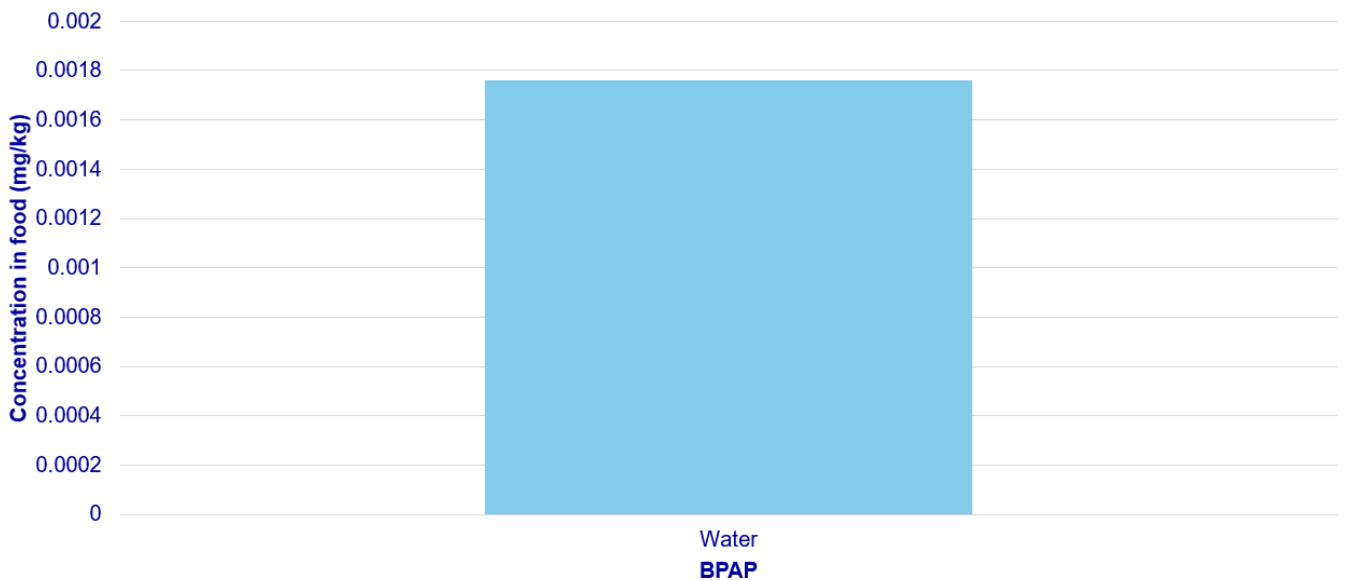


Figure 10: Vermeer FCM results for BPAP per food system – late innovation

The chemical concentrations in food predicted by Vermeer FCM were used as inputs to the INTEGRA model to provide the daily intake mean via ingestion. To assess the safety aspects of this use case and establish the corresponding RCRs, a toxicological threshold was necessary. The toxicological threshold in this case is the Tolerable Daily Intake (TDI), which is an estimate of a substance’s amount in food, air or drinking water that can be taken over a lifetime without appreciable health risks (EC, 2016). The results of the chemical risk assessment are described below.

4.3.2.1 Early Innovation

As previously mentioned, the VEGA models have been used to predict dose descriptor (NOAEL) for estimating toxicological thresholds in early innovation. In this case, two different approaches were employed. The first one is similar to the approach followed for DNELs. More specifically, the predicted NOAEL value from VEGA was used to calculate the TDIs of each substance, divided by an uncertainty factor. The second one is the application of the Threshold of Toxicological Concern (TTC) (Committee et al., 2019). To define the TTC of each chemical, the Cramer Classification method was utilized with the OECD QSAR toolbox. The classification showed that all three chemicals fall under the Cramer Class III

(high toxicity). This class corresponds to a TTC value of 1.5 µg/kg bw/day, which was applied to define the corresponding RCRs.

Table 75: Daily intake mean and RCRs calculated using Vermeer FCM results – Early Innovation

	Daily Intake mean (µg/kg bw)					
	Clear Drinks	Milk	Olive Oil	Orange Juice	Tomato Sauce	Water
BPA	0.010	0.005	4.39E-04	0.003	0.001	0.006
RCR (QSARs)	2.39E-04	1.10E-04	1.02E-05	7.38E-05	2.84E-05	1.51E-04
RCR (TTC)	6.67E-03	3.33E-03	2.93E-04	2.00E-03	6.67E-04	4.00E-03
BPAP	0.007	0.004	3.04E-04	0.003	8.53E-04	0.004
RCR (QSARs)	1.15E-04	6.04E-05	5.06E-06	4.25E-05	1.42E-05	6.57E-05
RCR (TTC)	4.67E-03	2.67E-03	2.03E-04	2.00E-03	5.69E-04	2.67E-03
Isosorbide	0.014	0.008	7.6E-04	0.005	0.002	0.009
RCR (QSARs)	3.47E-06	2.02E-06	1.95E-07	1.22E-06	4.22E-07	2.24E-06
RCR (TTC)	9.33E-03	5.33E-03	5.08E-04	3.33E-03	1.33E-03	6.00E-03

4.3.2.2 Late Innovation

In late innovation, the only chemical with available TDI value was BPA. In 2023, EFSA established a new TDI for BPA of 0.2 ng/kg bw/day (EFSA et al., 2023). This remarkably low TDI value is linked to the high RCRs for BPA, as shown in Table 76. Regarding BPAP, there was no available toxicological data for deriving a TDI. Thus, the toxicological thresholds used in late innovation were identical to the ones in early innovation. Finally, a self-derived TDI for Isosorbide was calculate by using the NOAEL value from a repeated dose oral toxicity study in rats available in the REACH dossier.

Table 76: Daily intake and RCRs calculated using Vermeer FCM results – Late Innovation

	Daily Intake mean (µg/kg bw)					
	Clear Drinks	Milk	Olive Oil	Orange Juice	Tomato Sauce	Water
BPA	0.010	0.005	4.39E-04	0.003	0.001	0.006
RCR	51.44	23.71	2.20	15.86	6.11	32.47
BPAP	0.006	0.003	3.014E-04	0.002	0.001	0.004
RCR (QSARs)	9.61E-05	5.26E-05	5.02E-06	4.24E-05	1.12E-05	6.1E-05
RCR (TTC)	3.84E-03	2.10E-03	2.01E-04	1.28E-03	4.46E-04	2.44E-03
Isosorbide	0.014	0.008	0.0007614	0.005	0.002	0.009
RCR	1.81E-05	1.05E-05	1.02E-06	6.37E-06	2.20E-06	1.17E-05

Overall, since the daily intakes for the two stages are identical (for BPA and Isosorbide), the characterization of the potential risks depends only on the magnitude of the relevant toxicological thresholds. For BPA, specifically, this magnitude is significantly lower than the predicted one. This difference emphasizes the importance of further evaluation and testing during the innovation process, as well as the need for developing more reliable tools for predicting the hazard potency.

4.3.3 CEM and INTEGRA – Epoxy resin application

Regarding the use case of epoxy paint, no general exposure scenario was given. Therefore, a default scenario included in the Consumer Exposure Model (CEM) v2.1 was utilized. CEM is an exposure assessment model that estimates indoor air and dust concentrations, as well as dermal and oral exposure to new and existing chemicals in consumer products and articles. CEM was employed to define the emissions rates of the exposure. The default scenario selected was the emission from a product in the category varnishes and floor finishes used by adults in full-time. With regard to the required physicochemical properties (molecular weight, vapor pressure, kow), they were predicted based on the chemical structure using the VEGA model (early innovation) or sourced from the ECHA and US CompTox databases. Moreover, a parameter that is scenario-specific and must be defined to perform the assessment is the weight fraction of the chemical in the product. To define the weight fraction of the chemical in product, a literature search was conducted. Based on that, we defined a weight fraction of 10^{-5} (10 ppm) for all the substances (Epoxy Resin Committee, 2015). The model provides the possibility to estimate the emission rates occurring from the product use. If measured input data is available, there is the possibility of entering user-defined emission rates.

The emission rates (see Figure 11-Figure 16) predicted by CEM were used as input to run INTEGRA. INTEGRA was used to estimate the acute inhalation exposure concentration and derive the respective RCRs. Regarding the use of toxicological thresholds, a similar approach to the previous steps was implemented. In early innovation, the DNELs for inhalation for consumers were estimated using the VEGA NOAEL value as previously described. In late innovation, the DNEL for BPA was retrieved from the REACH dossier. For Isosorbide, a NOAEL value from the REACH dossier was used to derive the respective DNEL for inhalation. Finally, for BPAP, the same toxicological thresholds were used for both innovation stages. To be noted, that due to lack of data for BPAP and Isosorbide, we used the long-term DNELs for RCR derivation.

4.3.3.1 Early Innovation

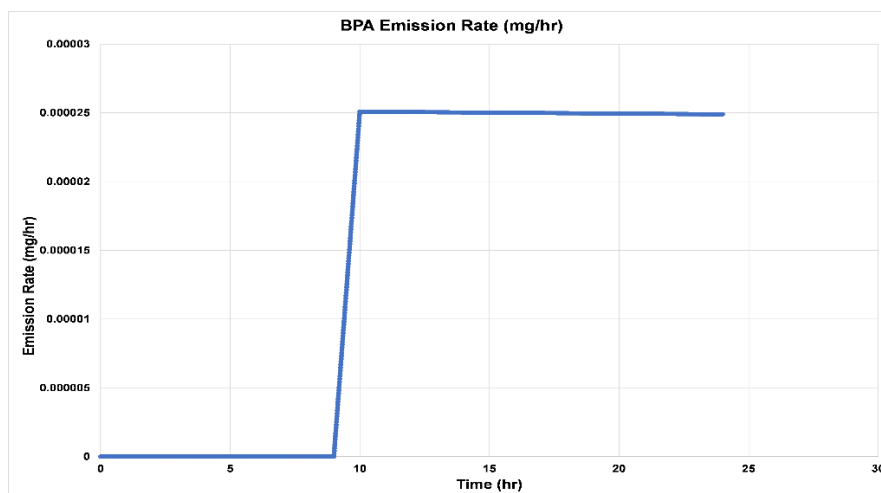


Figure 11: CEM results – BPA emission rate (mg/hr)

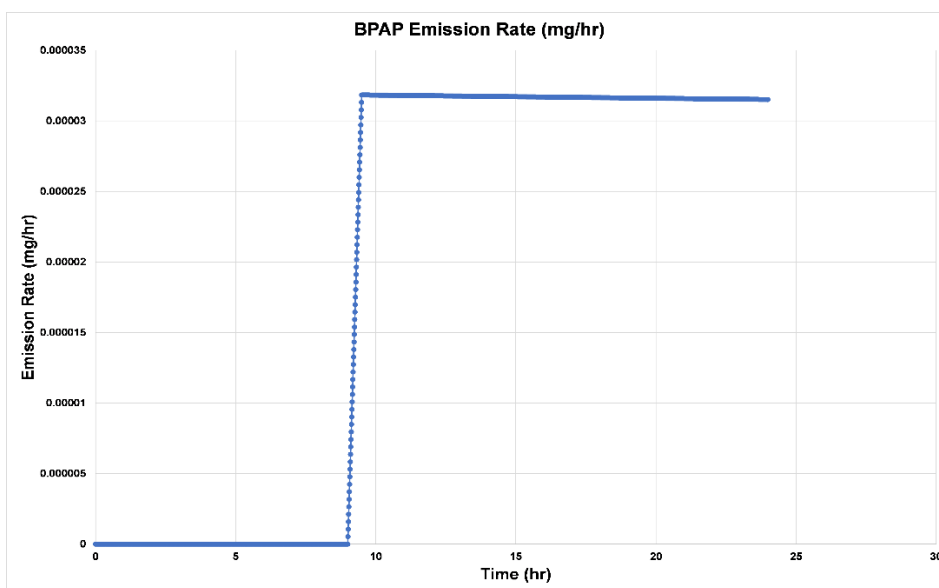


Figure 12: CEM results – BPAP emission rate (mg/hr)

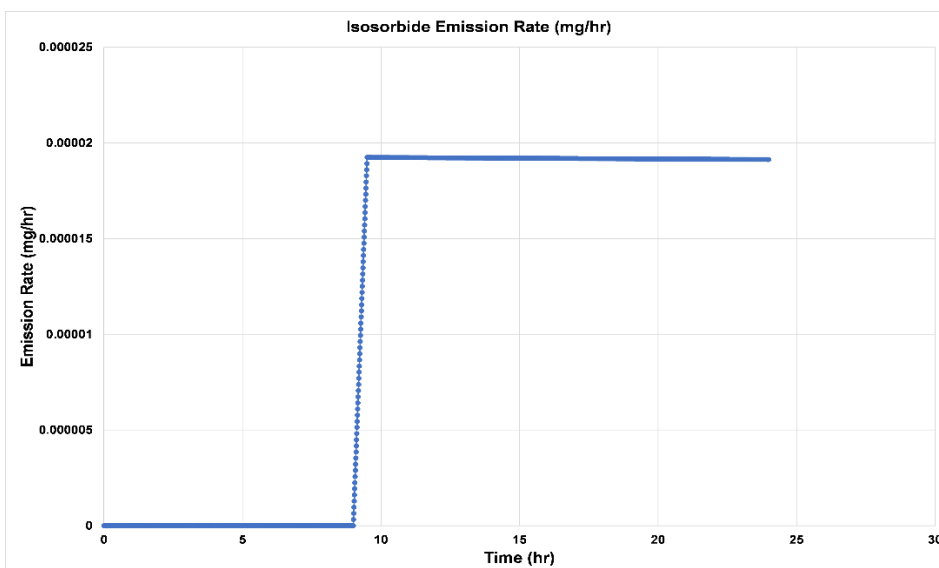


Figure 13: CEM results – Isosorbide emission rate (mg/hr)

Table 77: INTEGRA results using CEM results as input

	Acute inhalation exposure concentration (mg/m ³)	RCR
BPA	6.58E-08	2.63E-07
BPAP	8.33E-08	2.38E-07
Isosorbide	5.05E-08	2.18E-09

4.3.3.2 Late Innovation

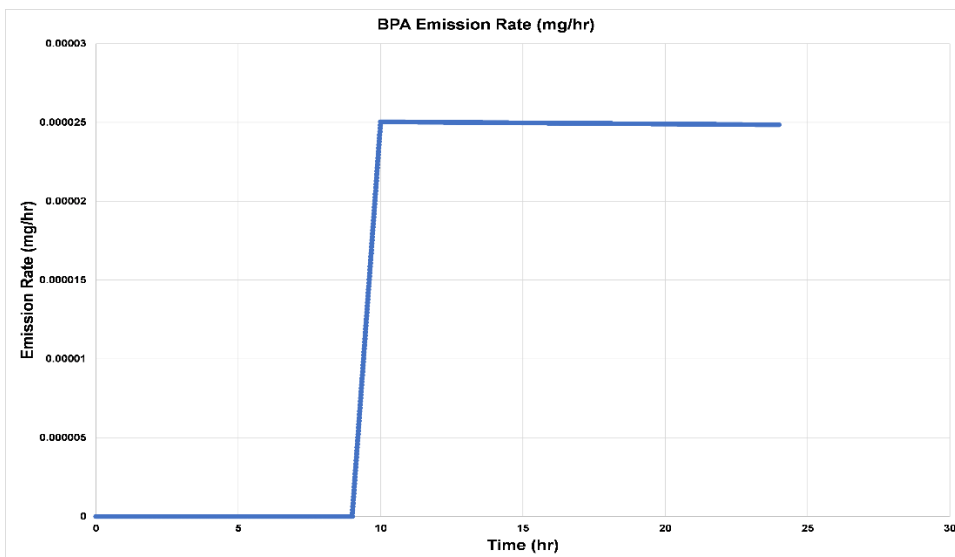


Figure 14: CEM results – BPA emission rate (mg/hr)

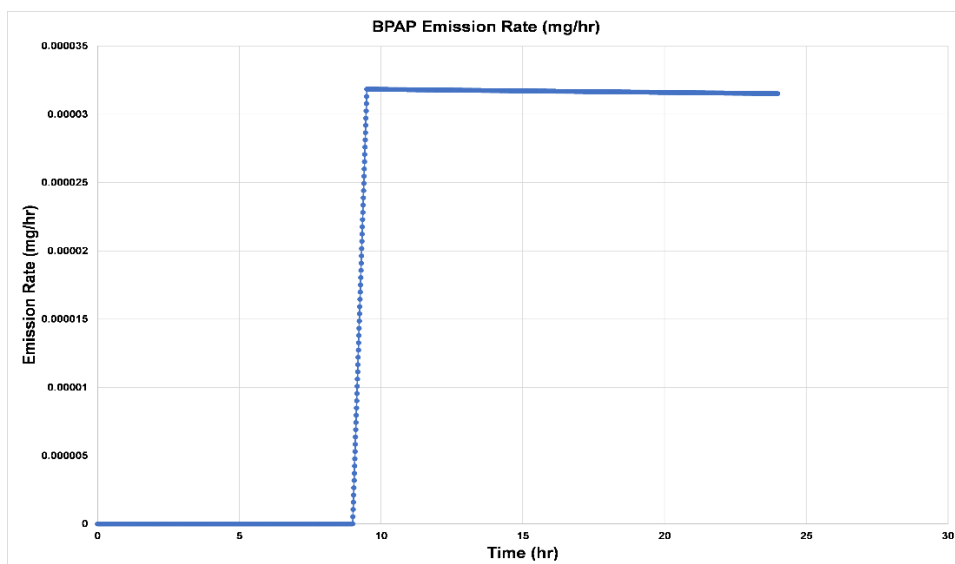


Figure 15: CEM results – BPAP emission rate (mg/hr)

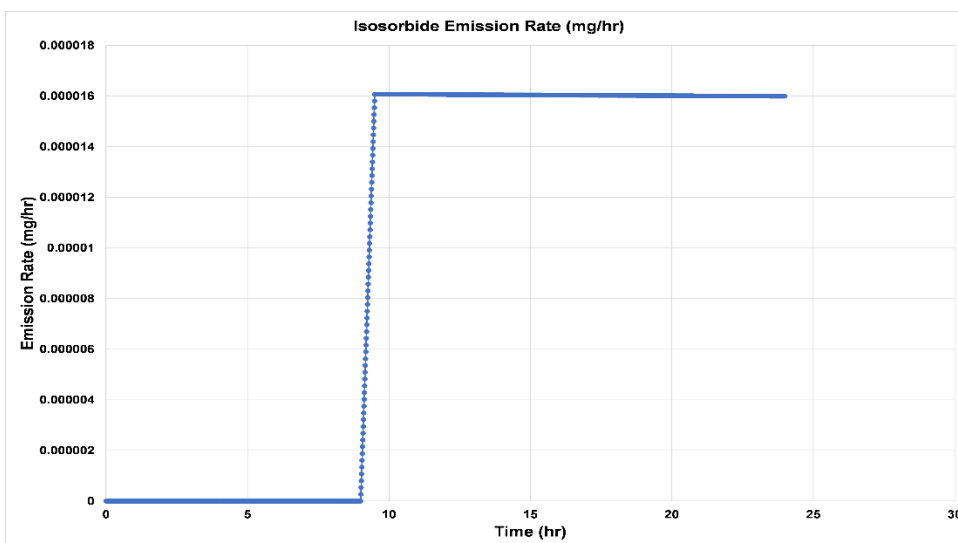


Figure 16: CEM results – Isosorbide emission rate (mg/hr)

Table 78: INTEGRA results using CEM results as input

	Acute inhalation exposure concentration (mg/m ³)	RCR
BPA	6.56E-08	6.56E-08
BPAP	8.33E-08	2.38E-07
Isosorbide	4.23E-08	1.42E-10

Based on the results provided, the exposure concentrations in both stages are very low. Therefore, considering also the values of DNELs used, this resulted in very low levels of RCRs. This could be mainly attributed to the weight of the fraction used for this specific scenario (10⁻⁵), as well as to the vapor pressure values of each substance. To conclude, the evaluation of consumer exposure during the SSbD assessment is scenario-specific and may differ from one application to another. Moreover, the choice of the tool to estimate the exposure occurring from the corresponding application could have an impact on the final outcomes. Finally, an uncertainty analysis of the tool outputs would be beneficial in order to gain a better understanding of the potential inaccuracies associated with the assessment process.

4.3.4 SSbD Score – Step 3

The scoring system followed in this step (Table 79) is based on the one suggested in the JRC SSbD case study (Caldeira et al., 2023). However, the indicators and criteria in Step 3 of SSbD are scenario-specific and depend on the use case under assessment.

Table 79: Scoring System for Step 3

Risk Characterization Ratio (RCR)	SSbD Score
> 1.5	0
1.1-1.5	1
0.5-1	2
<0.5	3

4.3.4.1 Polycarbonate application

The following scores are based on the results of Vermeer FCM and INTEGRA, As previously mentioned, the use of toxicological thresholds affect the magnitude of the final outcomes and the corresponding safety scores according to the JRC system. The case of BPA shows a notable discrepancy between these scores in early and late innovation. This discrepancy arises due to the significantly lower TDI value that has been established for BPA in late innovation. Therefore, it should be emphasized that the application of QSAR predictions should be approached conservatively for initial and screening assessment, when there is no available data.

4.3.4.1.1 Early innovation

Table 80: SSbD Score Step 3 – Early Innovation

	Water
BPA	3
BPAP	3
Isosorbide	3

4.3.4.1.2 Late innovation

Table 81: SSbD Score Step 3 – Late Innovation

	Water
BPA	0
BPAP	3

Isosorbide	3
-------------------	----------

4.3.4.2 Epoxy resin application

The following scores are based on the results of CEM and INTEGRA. Given that the resulting RCRs for each substance in both stages of innovation are below the threshold of 0.5, each substance has been assigned a score of 3.

4.3.4.2.1 Early innovation

Table 82: SSbD Score Step 3 – Early Innovation

	SSbD Score
BPA	3
BPAP	3
Isosorbide	3

4.3.4.2.2 Late innovation

Table 83: SSbD Score Step 3 – Late Innovation

	SSbD Score
BPA	3
BPAP	3
Isosorbide	3

4.4 Overall SSbD Score

Upon completion of the safety assessment for each SSbD step (Steps 1-3), a comprehensive evaluation of the overall SSbD performance was undertaken. The scoring system applied to the aggregation of the safety SSbD aspects was based on the one proposed by JRC. However, it should be noted that this scoring system is not definitive and is only used to aid communication and decision-making, as it has been stated in the JRC report (Caldeira et al., 2023). The overall SSbD score for Steps 1-3 was obtained by aggregating the scores of each safety step, as shown in the tables below.

- Step 1: it defines the hazard level of the chemical when applying the SSbD criteria for Step 1. The scores in this step range from 0 to 3, where 0 indicates the most hazardous. The score definition is based on the evaluation criteria of the SSbD framework.
- Step 2: it defines the potential risks arising from the manufacturing and processing of the chemical. The scores in this step range from 0 to 3 and are defined based on the magnitude of the total and individual RCRs of each contributing scenario for human health (HH) and the environment (ENV). An aggregation method is applied within Step 2 (see example Table 84).
- Step 3: it defines the potential risks arising from the final application of the chemical. The scores in this step range from 0 to 3 and their definition is scenario-specific. In the current case study, the score is based on the RCR resulting from the consumer exposure of each application. No aggregation method has been applied to this step.

Additionally, an aggregation of Steps 1-3 into a Hazard and Safety level was performed. The approach that was adopted for the aggregation entailed considering the minimum level among Steps 1-3 (see example

Table 85). Therefore, any chemical under assessment that obtains a score of 0 among Steps 1-3, is considered to have failed to meet any of the SSbD criteria, and as a result, is assigned the minimum score of 0. The results of the aggregation of Steps 1-3 for each application in both innovation stages are presented below.

4.4.1 Polycarbonate application

4.4.1.1 Early Innovation

Table 84: Aggregated Score for Step 2

	Manufacture		Polycarbonate Production		PC Bottle		Average	SSbD level Step 2
	HH	ENV	HH	ENV	HH	ENV		
BPA	0	0	0	1	1	0	0.33	0
BPAP	0	0	0	1	1	0	0.33	0
Isosorbide	3	3	3	3	3	3	3	3

Table 85: SSbD Score – Steps 1-3

	Hazard Level	Processing Level	Use phase Level	Worst level
BPA	0	0	3	0
BPAP	0	0	3	0
Isosorbide	INC	3	3	NA

4.4.1.2 Late Innovation

Table 86: Aggregated Score for Step 2

	Manufacture		Polycarbonate Production		PC Bottle		Average	SSbD level Step 2
	HH	ENV	HH	ENV	HH	ENV		
BPA	1	0	2	1	1	1	1	1
BPAP	1	0	2	0	1	0	0.67	1
Isosorbide	3	3	3	3	3	3	3	3

Table 87: SSbD Score – Steps 1-3

	Hazard Level	Processing Level	Use phase Level	Worst Level
BPA	0	1	0	0
BPAP	0	1	3	0
Isosorbide	3	3	3	3

4.4.2 Epoxy resin application

4.4.2.1 Early Innovation

Table 88: Aggregated Score for Step 2

	Manufacture		Epoxy resin Production		Epoxy paint		Average	SSbD level Step 2
	HH	ENV	HH	ENV	HH	ENV		
BPA	0	0	0	1	1	0	0.33	0
BPAP	0	0	0	0	1	0	0.17	0
Isosorbide	3	3	3	3	3	3	3	3

Table 89: SSbD Score – Steps 1-3

	Hazard Level	Processing Level	Use phase Level	Worst level
BPA	0	0	3	0
BPAP	0	0	3	0
Isosorbide	INC	3	3	NA

4.4.2.2 Late Innovation

Table 90: Aggregated Score for Step 2

	Manufacture		Epoxy resin Production		Epoxy paint		Average	SSbD level Step 2
	HH	ENV	HH	ENV	HH	ENV		
BPA	1	0	1	1	1	1	0.83	1
BPAP	1	0	1	0	1	0	0.5	0
Isosorbide	3	3	3	3	3	3	3	3

Table 91: SSbD Score – Steps 1-3

	Hazard Level	Processing Level	Use phase Level	Worst Level
BPA	0	1	3	0
BPAP	0	0	3	0
Isosorbide	3	3	3	3

4.5 Step 4 – Environmental sustainability assessment

For step 4 of the SSbD framework, life cycle assessment (LCA) was performed with different tools. The assessment was conducted on polycarbonate bottles made from BPA, BPAP and isosorbide.

One of the tools applied is a common LCA software, GaBi (LCA for experts), available from Sphera Solutions. GaBi is a widely used commercial software containing proprietary and confidential datasets on various industrial processes. At the same time, a less well-known model was also applied: quasaLCA, a new LCA model developed by the Norwegian climate and environmental research institute NILU. Both GaBi and quasaLCA allow practitioners to gather impact results with various life cycle impact assessment (LCIA) methods. Here, Environmental Footprint 3.0 was the main method applied, as recommended by the European Commission (Commission et al., 2022). Therefore, the impact categories recommended by the EC were selected. The work in the BPA & alternatives case study allowed for discussions on the differences in the assessment when applying different LCA tools.

Additionally, a life cycle impact assessment focusing on human toxicity for workers was performed using ProScale. ProScale provides a hazard and exposure-based quantitative scoring system for comparing direct chemical risks (corresponding to near-field human toxicity) to workers, professionals and consumers associated with products in a life cycle perspective (Rydberg et al., 2017). The scores provided by ProScale do not directly correlate to the indicators provided by the EF method, as they are an indication of direct human exposure to chemical risks throughout all processes in the life cycle of a product. ProScale is a valuable asset to perform a step 2 assessment with a life cycle perspective. However, since the impacts are assessed throughout the life cycle of products, the tool is also relevant for step 4 and thus mentioned in this section.

4.5.1 GaBi

Screening Life Cycle Assessment (LCA) was conducted for early phase assessment of the environmental impacts of the chemicals. The LCA looked at the cradle-to-gate (raw material acquisition to polycarbonate production) production of polycarbonate powders based on BPA, BPAP, and isosorbide respectively (Figure 4 - Figure 6, Section 2.3.1). The use phase and end-of-life will be added in the forthcoming final case study report. The system models were created as if processes for synthesizing BPA, BPAP,

isosorbide, as well as polycarbonates synthesized from each of them, did not exist yet. Consequently, the assessment required assumptions for the mass and energy balance of the chemicals' life cycles. The aim was to test how to perform LCA in early stages of innovation.

4.5.1.1 Modelling

To illustrate which unit processes were modelled manually (and thus required assumptions based on mass and energy balances) and which were modelled using GaBi datasets, the following three tables list all processes from the model. Each table includes a description that links the unit process/flow to the flowcharts illustrated in (Figure 4 - Figure 6, Section 2.3.1). Inputs and outputs, including assumed emissions, of the manually modelled processes are listed in Table 95. Mass flows of inputs and products were calculated via stoichiometric mass balances and chemical losses were added (using a re-calculation factor to account for losses).

Table 92. Summary of processes used in the model of BPA based polycarbonate including those which were modelled manually. All unit processes relate to unit processes and/or flows in Figure 4 (phase 1 and 2).

Entry	Process	Dataset used in model	Reference	Description
1	Production of BPA based PC (<i>gate-to-gate</i>)	Manually modelled	Stoichiometric mass balances and release factors from ERCs	Polycarbonate via interfacial polycondensation (gate-process of the LCA)
2	Sodium hydroxide (<i>cradle-to-gate</i>)	Sodium hydroxide (100% NaOH) (EU-28)	Sphera	Auxiliary input to polycarbonate production
3	Water (<i>cradle-to-gate</i>)	RER: Water (deionized)	Sphera	Input to BPA production
4	Phosgene (<i>cradle-to-gate</i>)	RER: phosgene production, liquid	ecoinvent	Input to polycarbonate production
5	Dichloromethane (<i>cradle-to-gate</i>)	RER: dichloromethane production	ecoinvent	Auxiliary input to polycarbonate production
6	BPA production (<i>gate-to-gate</i>)	Manually modelled	Stoichiometric mass balances and release factors from ERCs	Input to polycarbonate production
7	Ethanol (<i>cradle-to-gate</i>)	Ethanol (96%) from ethylene hydration	Sphera	Auxiliary input to BPA production
8	Phenol (<i>cradle-to-gate</i>)	Phenol (EU-28)	Sphera	Input to BPA production
9	Acetone (<i>cradle-to-gate</i>)	Acetone (EU-28)	Sphera	Input to BPA production
10	WWTP (<i>gate-to-grave</i>)	RER: Municipal wastewater treatment	Sphera	Wastewater output from polycarbonate production
11	Electricity	EU-28: Electricity production	Sphera	Energy input to several unit processes
12	Thermal energy	Thermal energy from natural gas (EU-28)	Sphera	Energy input to several unit processes
13	Transports	GLO: Truck, Euro 6 A-C, 28-32t gross	Sphera	Between all unit processes where

		weight / 22t payload capacity		transports are anticipated Parameters per transport: Distance: 1126km Load factor: 0.85 Sulfur content: 4
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Table 93. Summary of processes used in the model of BPAP based polycarbonate including those which were modelled manually. All unit processes relate to unit processes and/or flows in Figure 5 (phase 1 and 2).

Entry	Process	Dataset in GaBi	Reference	Description
1	Production of BPAP based PC (<i>gate-to-gate</i>)	Manually modelled	Stoichiometric mass balances and release factors from ERCs	Polycarbonate via interfacial polycondensation (gate-process of the LCA)
2	Phosgene (<i>cradle-to-gate</i>)	RER: phosgene production, liquid	ecoinvent	Input to polycarbonate production
3	Dichloromethane (<i>cradle-to-gate</i>)	RER: dichloromethane production	ecoinvent	Auxiliary input to polycarbonate production
4	BPAP production (<i>gate-to-gate</i>)	Manually modelled	Stoichiometric mass balances and release factors from ERCs	Input to polycarbonate production
5	Water (<i>cradle-to-gate</i>)	RER: Water (deionized)	Sphera	Input to polycarbonate production
6	WWTP (<i>gate-to-grave</i>)	RER: Municipal wastewater treatment	Sphera	Wastewater output from polycarbonate production
7	Acetophenone (<i>gate-to-gate</i>)	Manually modelled	Stoichiometric mass balances and release factors from ERCs	Input to BPAP production
8	Phenol (<i>cradle-to-gate</i>)	Phenol (EU-28)	Sphera	Input to BPAP production
9	Cumene (<i>cradle-to-gate</i>)	RER: Cumene (isopropylbenzene)	Sphera	Input to acetophenone production
10	Oxygen (<i>cradle-to-gate</i>)	Oxygen (gaseous) (EU-28)	Sphera	Auxiliary input to acetophenone production
11	Electricity	EU-28: Electricity production	Sphera	Energy input to several unit processes
12	Thermal energy	Thermal energy from natural gas (EU-28)	Sphera	Energy input to several unit processes
13	Transports	GLO: Truck, Euro 6 A-C, 28-32t gross weight / 22t payload capacity	Sphera	Between all unit processes where transports are anticipated Parameters per transport:

				Distance: 1126km Load factor: 0.85 Sulfur content: 4
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Table 94. Summary of processes used in the model of isosorbide-based polycarbonate including those which were modelled manually. All unit processes relate to unit processes and/or flows in Figure 6 (phase 1 and 2).

Entry	Process	Dataset used in model	Reference	Description
1	Production of IS based PC (<i>gate-to-gate</i>)	Manually modelled	Stoichiometric mass balances and release factors from ERCs	Polycarbonate via interfacial polycondensation* (gate-process of the LCA)
2	Sodium hydroxide (<i>cradle-to-gate</i>)	Sodium hydroxide (100% NaOH) (EU-28)	Sphera	Auxiliary input to polycarbonate production
3	Phosgene (<i>cradle-to-gate</i>)	RER: phosgene production, liquid	ecoinvent	Input to polycarbonate production**
4	Dichloromethane (<i>cradle-to-gate</i>)	RER: dichloromethane production	ecoinvent	Auxiliary input to polycarbonate production
5	Water (<i>cradle-to-gate</i>)	RER: Water (deionized)	Sphera	Input to polycarbonate production and sorbitol production
6	WWTP (<i>gate-to-grave</i>)	RER: Municipal wastewater treatment	Sphera	Wastewater output from polycarbonate production
8	Isosorbide production (<i>gate-to-gate</i>)	Manually modelled	Stoichiometric mass balances and release factors from ERCs	Input to polycarbonate production
9	Sulfuric acid (<i>cradle-to-gate</i>)	RER: Sulphuric acid (100% H ₂ SO ₄)	Fertilizers Europe	Auxiliary input to isosorbide production
10	Sorbitol production (<i>gate-to-gate</i>)	Manually modelled	Stoichiometric mass balances and release factors from ERCs	Input to isosorbide production
11	Glucose (<i>cradle-to-gate</i>)	RER: glucose production	Ecoinvent	Input to sorbitol production
12	Hydrogen (<i>cradle-to-gate</i>)	DE: Hydrogen (steam reforming natural gas)	Sphera	Auxiliary input to sorbitol production
13	Electricity	EU-28: Electricity production	Sphera	Energy input to several unit processes
14	Thermal energy	Thermal energy from natural gas (EU-28)	Sphera	Energy input to several unit processes
15	Transports	GLO: Truck, Euro 6 A-C, 28-32t gross weight / 22t payload capacity	Sphera	Between all unit processes where transports are anticipated Parameters per transport:

				Distance: 1126km Load factor: 0.85 Sulfur content: 4
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*Polymerization process of polycarbonate from isosorbide was assumed to be interfacial polycondensation as for BPA and BPAP instead of melt polymerization for simplicity.

**Process not included in Figure 6 because of above assumption.

Table 95. Inputs and outputs, including assumed emissions, used in the manually modelled processes.

Flow	Value	Unit	Description
Production of BPA based PC (Table 92, entry 1)			
BPA	1.06	kg	Input
Electricity	0.41	MJ	
Phosgene	0.48	kg	
Sodium hydroxide	0.39	kg	
Dichloromethane	12.33	kg	
Polycarbonate (BPA based)	1.00	kg	Output
Sodium chloride	0.46	kg	
Bisphenol A [Organic emissions to fresh water]	0.046	kg	
Phosgene [Organic emissions to sea water]	0.01	kg	
Phosgene [Organic emissions to fresh water]	0.01	kg	
Phosgene [Halogenated organic emissions to air]	0.02	kg	
Sodium hydroxide [Inorganic emissions to air]	0.02	kg	
Sodium chloride (rock salt) [Inorganic emissions to fresh water]	0.03	kg	
Wastewater (contaminated with methyl chloride)	16.38	kg	
Dichloromethane (methylene chloride) [Halogenated organic emissions to air]	0.12	kg	
BPA production (Table 92, entry 6)			
Acetone	0.31	kg	Input
Electricity	1.67	MJ	
Phenol	0.99	kg	
Thermal energy	2.61	MJ	
Solvent (EtOH assumed)	1.7	kg	
Water	15.6	kg	
BPA	1	kg	Output
Acetone (dimethyl ketone) [Organic emissions to industrial soil]	0.0001	kg	
Acetone (dimethyl ketone) [Organic emissions to sea water]	0.00261	kg	
Acetone (dimethyl ketone) [Organic emissions to agricultural soil]	0.0001	kg	
Acetone (dimethyl ketone) [Group NMVOC to air]	0.01	kg	
Acetone (dimethyl ketone) [Organic emissions to fresh water]	0.003	kg	
Bisphenol A [Organic emissions to fresh water]	0.06	kg	
Phenol (hydroxy benzene) [Organic emissions to industrial soil]	0.0004	kg	
Phenol (hydroxy benzene) [Hydrocarbons to sea water]	0.008	kg	
Phenol (hydroxy benzene) [Hydrocarbons to fresh water]	0.008	kg	
Phenol (hydroxy benzene) [Group NMVOC to air]	0.04	kg	
Phenol (hydroxy benzene) [Organic emissions to agricultural soil]	0.0004	kg	
Ethanol [Group NMVOC to air]	0.09	kg	
Production of BPAP based PC (Table 93, entry 1)			
BPAP	1.09	kg	Input
Phosgene	0.39	kg	
Thermal energy	6.72	MJ	
Electricity	0.41	MJ	
Dichloromethane	12.55	kg	
Water	6.24	kg	
Sodium hydroxide	0.32	kg	
Polycarbonate (BPAP based)	1	kg	Output
Sodium chloride	0.37	kg	

Phosgene [Organic emissions to fresh water]	0.008	kg	
Phosgene [Halogenated organic emissions to air]	0.02	kg	
Phosgene [Organic emissions to sea water]	0.008	kg	
Wastewater	16.7	kg	
Dichloromethane (methylene chloride) [Halogenated organic emissions to air]	0.12	kg	
Sodium chloride (rock salt) [Inorganic emissions to fresh water]	0.02	kg	
Sodium hydroxide [Inorganic emissions to air]	0.01	kg	
BPAP production (Table 93, entry 4)			
Phenol	1.13	kg	Input
Acetophenone	0.72	kg	
Electricity	1.67	MJ	
Thermal energy	2.61	MJ	
BPAP	1	kg	Output
Acetophenone [Group NMVOC to air]	0.03	kg	
Phenol (hydroxy benzene) [Organic emissions to industrial soil]	0.00005	kg	
Phenol (hydroxy benzene) [Hydrocarbons to sea water]	0.03	kg	
Phenol (hydroxy benzene) [Hydrocarbons to fresh water]	0.03		
Phenol (hydroxy benzene) [Group NMVOC to air]	0.05	kg	
Phenol (hydroxy benzene) [Organic emissions to agricultural soil]	0.00005	kg	
Acetophenone (Table 93, entry 7)			
Cumene	0.32	kg	Input
Oxygen	1.18	kg	
Electricity	1.11	MJ	
Acetophenone	1	kg	Output
Methanol	0.27	kg	
Acetophenone [Group NMVOC to air]	0.05	kg	
Cumene (isopropylbenzene) [Organic emissions to industrial soil]	0.0001	kg	
Cumene (isopropylbenzene) [Organic emissions to sea water]	0.003	kg	
Cumene (isopropylbenzene) [Organic emissions to fresh water]	0.003	kg	
Cumene (isopropylbenzene) [Organic emissions to agricultural soil]	0.0001	kg	
Cumene (isopropylbenzene) [Group NMVOC to air]	0.01	kg	
Methanol [Organic emissions to industrial soil]	0.00001	kg	
Methanol [Hydrocarbons to sea water]	0.01	kg	
Methanol [Organic emissions to agricultural soil]	0.00001	kg	
Methanol [Group NMVOC to air]	0.01	kg	
Methanol [Hydrocarbons to fresh water]	0.01	kg	
Production of IS based PC (Table 94, entry 1)			
Isosorbide	1.01	kg	Input
Electricity	0.56	MJ	
Phosgene	0.71	kg	
Polycarbonate (isosorbide base-d)	1	kg	Output
Sodium chloride	0.46	kg	
Phosgene [Organic emissions to sea water]	0.01	kg	
Phosgene [Organic emissions to fresh water]	0.01	kg	
Phosgene [Halogenated organic emissions to air]	0.03	kg	
Sodium hydroxide [Inorganic emissions to air]	0.02	kg	
Sodium chloride (rock salt) [Inorganic emissions to fresh water]	0.04	kg	
Wastewater (contaminated with methyl chloride)	15.48	kg	
Dichloromethane (methylene chloride) [Halogenated organic emissions to air]	0.12	kg	
Isosorbide production (Table 94, entry 8)			
Sorbitol	1.47	kg	Input
Electricity	1.11	MJ	
Sulfuric acid	0.79	kg	
Thermal energy	5.56	MJ	

Isosorbide	1	kg	Output
Sorbitol [Organic emissions to industrial soil]	0.0006	kg	
Sorbitol [Organic emissions to sea water]	0.01	kg	
Sorbitol [Organic emissions to agricultural soil]	0.0006	kg	
Sorbitol [Group NMVOC to air]	0.06	kg	
Sorbitol [Organic emissions to fresh water]	0.01	kg	
Isosorbide [Organic emissions to fresh water]	0.03	kg	
Sulfuric acid [Inorganic emissions to air]	0.0003	kg	
Sulfuric acid [Inorganic emissions to fresh water]	0.007	kg	
Sulfuric acid [Inorganic emissions to sea water]	0.007	kg	
Sorbitol production (Table 94, entry 10)			
Glucose	1.17	kg	Input
H2	0.01	kg	
Electricity	0.88	MJ	
Heat	0.95	MJ	
Water	1.64	kg	
Sorbitol	1	kg	Output
Glucose [Organic emissions to air]	0.05	kg	
Glucose [Organic emissions to fresh water]	0.01	kg	
Glucose [Organic emissions to sea water]	0.01	kg	
Hydrogen [Inorganic emissions to air]	0.001	kg	

Emissions from input and output flows in the manually modelled processes were estimated using default worst case release factors based on Environmental Release Categories (ERCs) and Specific ERCs (SpERCs) as proposed by ECHA for environmental exposure assessment within REACH (ECHA, 2016). To model emissions from solvents, the SpERCs developed by the European Solvents Industry Group were applied (ESIG, 2018).

Table 96 Summary of emissions calculated for processes in the BPA system.

BPA-PC production				
Release factors	Mass flow (kg/FU)	Emission to air	Emission to water	Emission to soil
ERC6C - Use of monomer in polymerisation		5%	5%	0%
Phosgene	0.431	0.02155	0.02155	0
Bisphenol A	0.995	0	0.04975	0
ERC6A - Use of intermediate		5%	2%	0.10%
Sodium hydroxide	0.349	0.01745	0.00698	0.000349
ERC1 - Manufacture of the substance		5%	6%	0.01%
Polycarbonate	1	0	0.06	0.0001
NaCl	0.46	0	0.0276	0.000046
SpERC solvents - DCM		5%	1.00%	0.01%
Dichloromethane	11.94	0.597	0.1194	0.001194
BPA production				
Release factors	Mass flow (kg/FU)	Emission to air	Emission to water	Emission to soil
ERC6A - Use of intermediate		5%	2%	0.10%
Acetone	0.282	0.0141	0.00564	0.000282
Phenol	0.914	0.0457	0.01828	0.000914
ERC1 - Manufacture of the substance		5%	6%	0.01%
Bisphenol A	1	0	0.06	0.0001
SpERC solvents - EtOH		5%	1.00%	0.01%
EtOH	2.91	0.1455	0.0291	0.000291

Table 97 Summary of emissions calculated for processes in the BPAP system

BPAP-PC production				
Release factors	Mass flow (kg/FU)	Emission to air	Emission to water	Emission to soil
ERC1 - Manufacture of the substance		5%	6%	0.01%
Polycarbonate	1	0.05	0.06	0.0001
NaCl	0.369	0.01845	0.02214	0.0000369
ERC6C - Use of monomer in polymerisation		5%	5%	0.00%
Bisphenol AP	0.937	0.04685	0.04685	0
Phosgene	0.319	0.01595	0.01595	0
Sodium hydroxide	0.258	0.0129	0.0129	0
SpERC solvents - DCM		5%	1.00%	0.01%
Dichloromethane	2.4	0.12	0.024	0.00024
BPAP production				
Release factors	Mass flow (kg/FU)	Emission to air	Emission to water	Emission to soil
ERC6A - Use of intermediate		5%	6%	0.01%
Acetophenone	0.591	0.02955	0.03546	0.0000591
Phenol	0.926	0.0463	0.05556	0.0000926
ERC1 - Manufacture of the substance		5%	6%	0.01%
BPAP	1	0.05	0.06	0.0001
Acetophenone production				
Release factors	Mass flow (kg/FU)	Emission to air	Emission to water	Emission to soil
ERC6A - Use of intermediate		5%	2%	0.10%
Cumene	0.27	0.0135	0.0054	0.00027
Oxygen	1	0.05	0.02	0.001
ERC1 - Manufacture of the substance		5%	6%	0.01%
Acetophenone	1	0.05	0.06	0.0001
MeOH	0.27	0.0135	0.0162	0.000027

Table 98 Summary of emissions calculated for processes in the isosorbide system.

Isosorbide-PC production				
Release factors	Mass flow (kg/FU)	Emission to air	Emission to water	Emission to soil
ERC6C - Use of monomer in polymerisation		5%	5%	0%
Phosgene	0.587	0.02935	0.02935	0.0000000
Isosorbide	0.869	0.04345	0.04345	0.0000000
Sodium hydroxide	0.475	0.02375	0.02375	0.0000000
ERC1 - Manufacture of the substance		5%	6%	0.01%
Polycarbonate	1	0.05	0.06	0.0001
NaCl	0.679	0.03395	0.04074	0.0000679
SpERC solvents - DCM		5%	1.00%	0.01%
Dichloromethane	2.4	0.12	0.024	0.00024
Isosorbide production				
Release factors	Mass flow (kg/FU)	Emission to air	Emission to water	Emission to soil
ERC6A - Use of intermediate		5%	2%	0.10%
Sorbitol	1.24652735	0.062326368	0.024930547	0.001246527
Sulfuric acid	0.671121238	0.033556062	0.013422425	0.000671121
ERC1 - Manufacture of the substance		5%	6%	0.01%
Isosorbide	1	0.05	0.06	0.0001
Sorbitol production				
Release factors	Mass flow (kg/FU)	Emission to air	Emission to water	Emission to soil
ERC6A - Use of intermediate		5%	2%	0.10%
Glucose	0.989	0.04945	0.01978	0.000989
Hydrogen	0.011	0.00055	0.00022	0.000011
ERC1 - Manufacture of the substance		5%	6%	0.01%
Sorbitol	1	0.05	0.06	0.0001

4.5.1.2 Results and discussion

Figure 17 illustrates a comparison of the environmental impacts of the assessed polycarbonate products using the Life Cycle Impact Assessment (LCIA) method EF 3.0, focussing on 13 midpoint environmental impact indicators. Terrestrial and marine eutrophication and ionic radiation were not included in the graph. Impact categories were normalised to 100% impact per impact category.

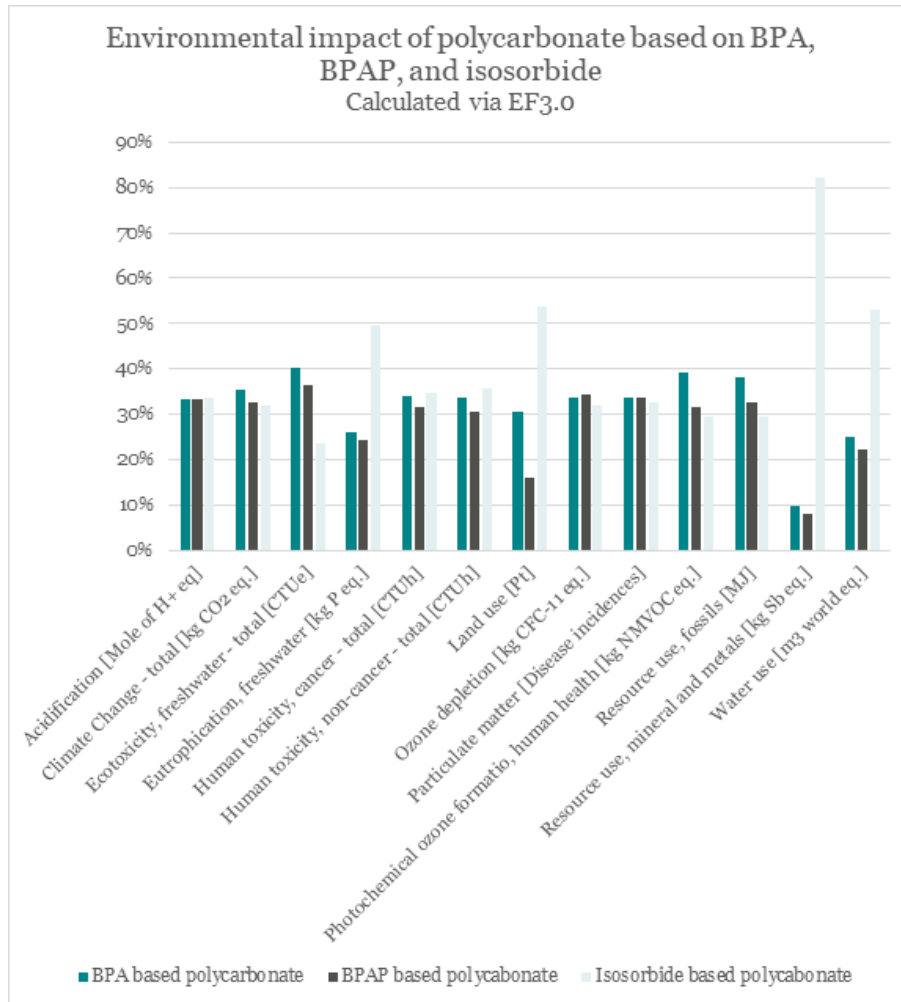


Figure 17: Cradle-to-gate environmental impact of polycarbonate based on BPA, BPAP and isosorbide respectively, calculated via EF 3.0 and normalized to 100% impact per midpoint impact category.

The LCIA results show that in approximately half of the indicators there seems to be no significant difference between the three polycarbonate alternatives. For the remaining indicators there are larger differences, for example isosorbide-based polycarbonate shows higher impacts in four impact categories: Eutrophication, Land use, Resource use (mineral and metals) and Water use.

Figure 18- Figure 20 illustrate hot-spot analysis for the three alternatives. One can observe that the use of dichloromethane as a solvent in the production of polycarbonate is heavily dominating in most of the impact categories.

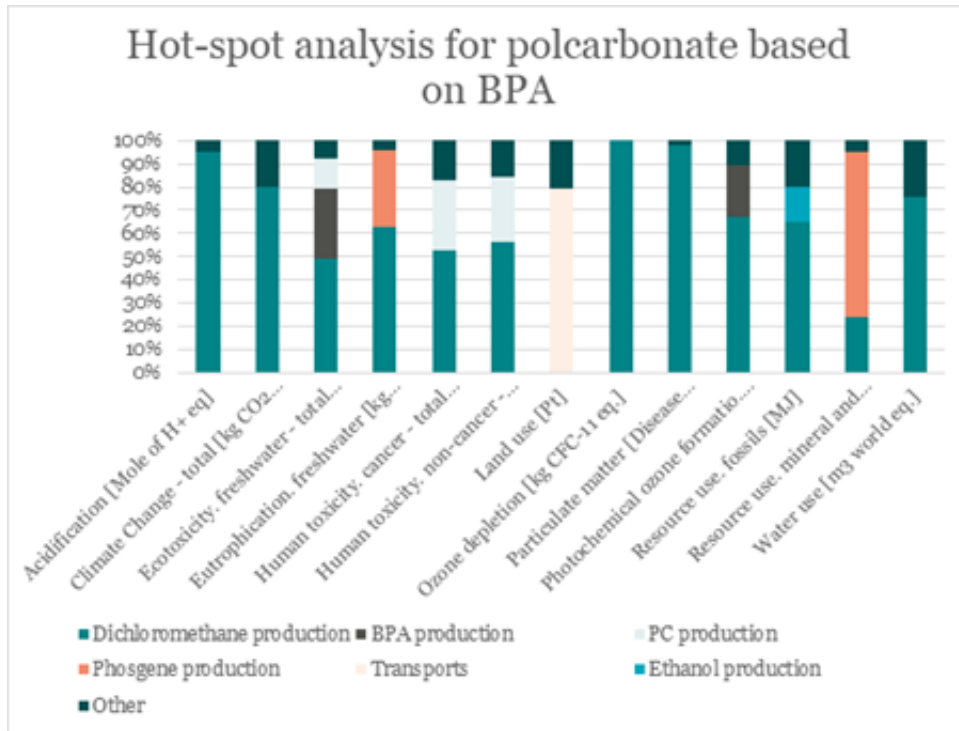


Figure 18: Hot-Spot analysis for the cradle-to-gate environmental impact of polycarbonate based on BPA, calculated via EF 3.0 and normalized to 100% per midpoint impact category

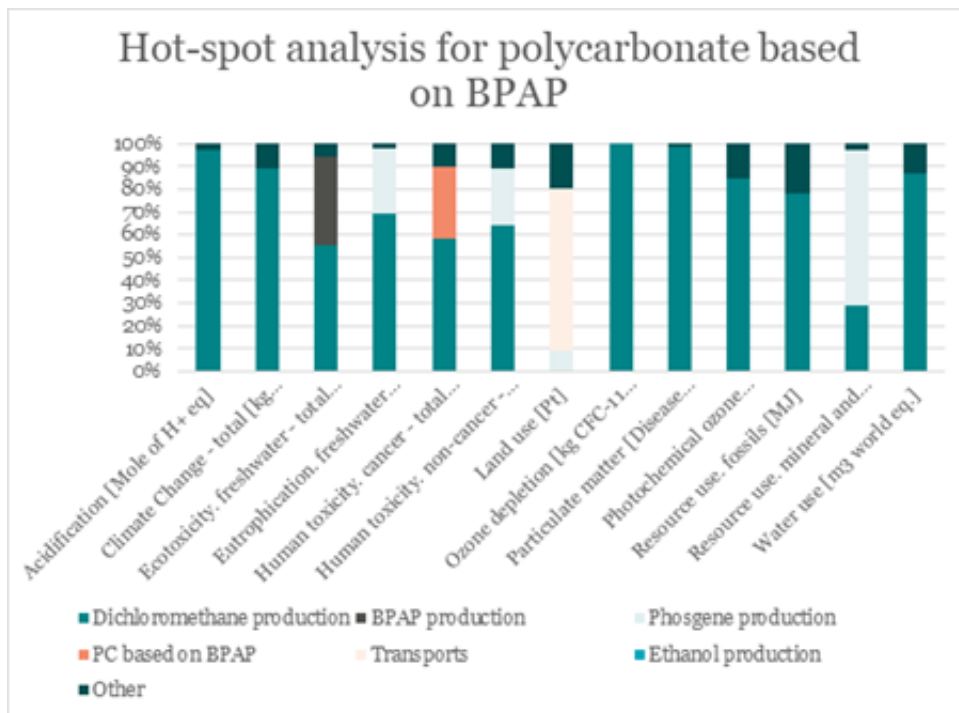


Figure 19: Hot-spot analysis for the cradle-to-gate environmental impact of polycarbonate based on BPAP, calculated via EF 3.0 and normalized to 100% impact per midpoint impact category.

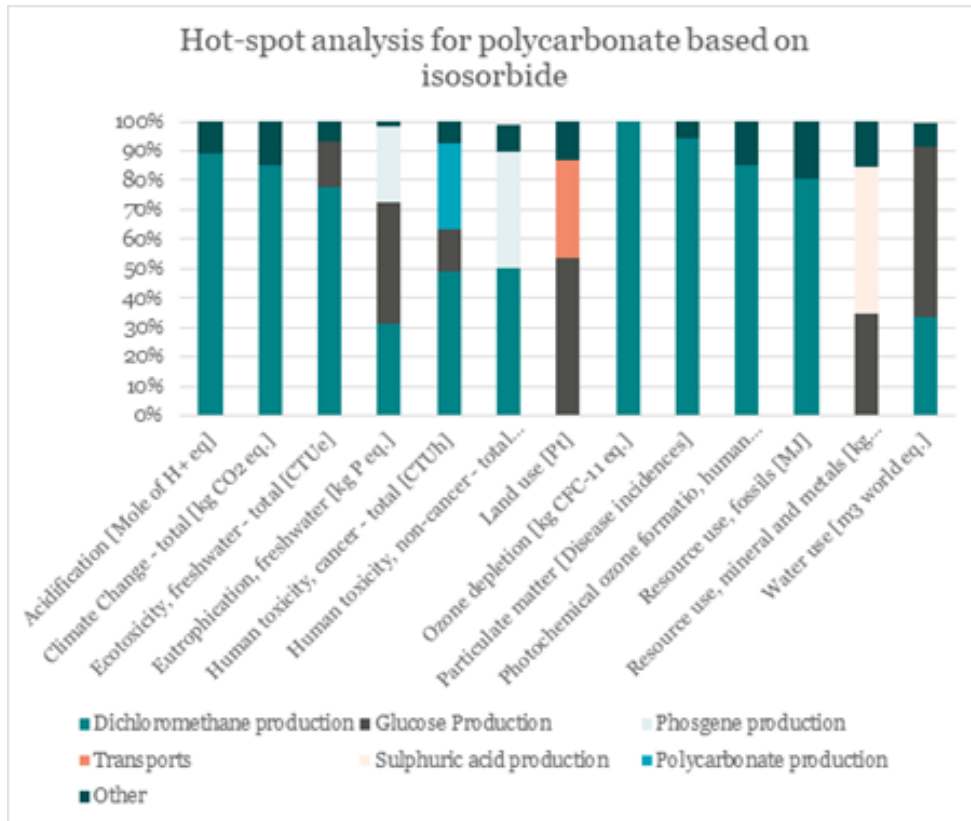


Figure 20: Hot-spot analysis for the cradle-to-gate environmental impact of polycarbonate based on isosorbide, calculated via EF 3.0 and normalized to 100% impact per midpoint impact category.

4.5.1.3 Comparison with reference results

The results of the screening LCA were compared with results based on primary data (Figure 21). A comparison was made between the environmental impacts of polycarbonate from BPA modelled in this study (LCI according to Table 95) versus the BPA production model from a standard LCA database (here from the GaBi database; the model is based on a typical production process on the market). The gap in the impact is on average 10%, varying in a range of 1-34% depending on the impact category. However, the results from a screening LCA can already be a good indication of the environmental impact of a chemical.

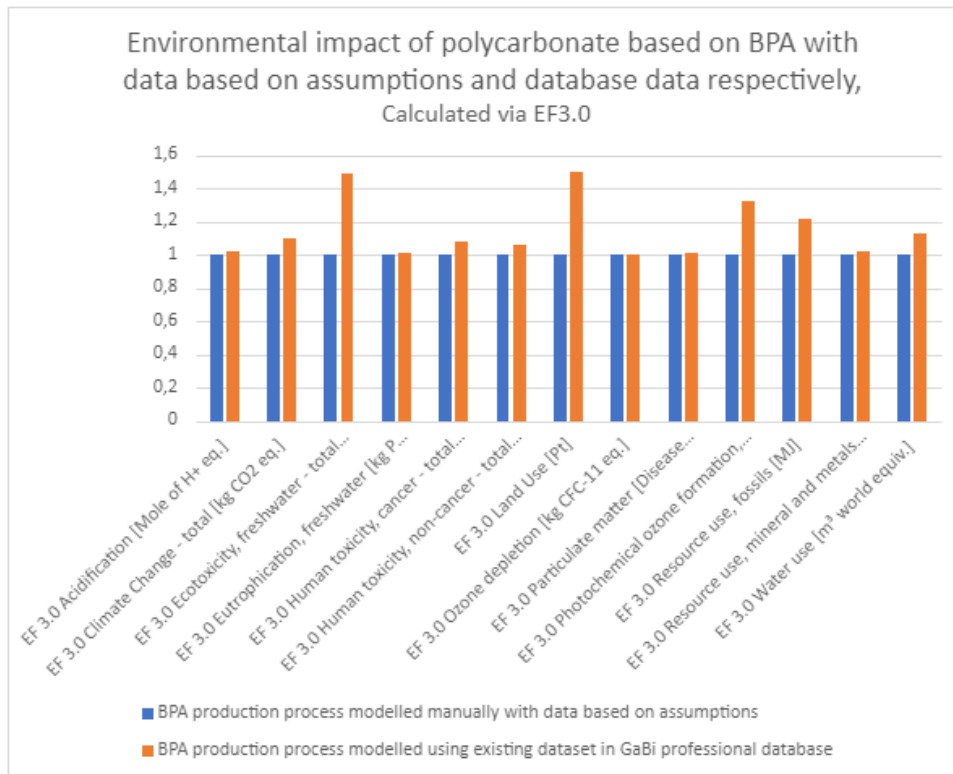


Figure 21: Environmental impact comparison of polycarbonate based on BPA with data based on assumptions and database data respectively. Calculated via EF 3.0.

4.5.2 Ecoinvent/quasaLCA

4.5.2.1 Approach

NILUs has developed the in-house model quasaLCA, a python model aimed at performing rapid LCA calculations and aimed at inclusion in digital workflows.

The purpose here was to test how well quasaLCA could be used for the assessment of individual chemical production routes in the SSbD context, and in rather early stages of innovation, rather than provide an extensive LCA study of the process routes. Based on the lifecycle inventory background database ecoinvent v3.8 – cut-off model¹ as well as data published in literature, the foreground system for the two synthesis routes of BPA and isosorbide has been modeled and connected to a bottle production process. The footprint associated with the production, use and end-of-life (EOL) of one bottle for each of the synthesis routes was calculated and contribution analysis was applied to further investigate the contributions of individual processes as well as direct and indirect contributions to environmental footprints for the individual foreground processes modelled. The impact assessment model used by default in quasaLCA is ReCiPe 2016, but here we present results computed with Environmental Footprint v3.

The study focuses on the production of 1 plastic bottle made of polycarbonate from BPA or its alternative - isosorbide, its use and its disposal at EOL. The production and use are assumed to be respectively in Germany and Western Europe. Transportation between processes is not included in the base model,

but the effect of transportation is presented in the discussion.

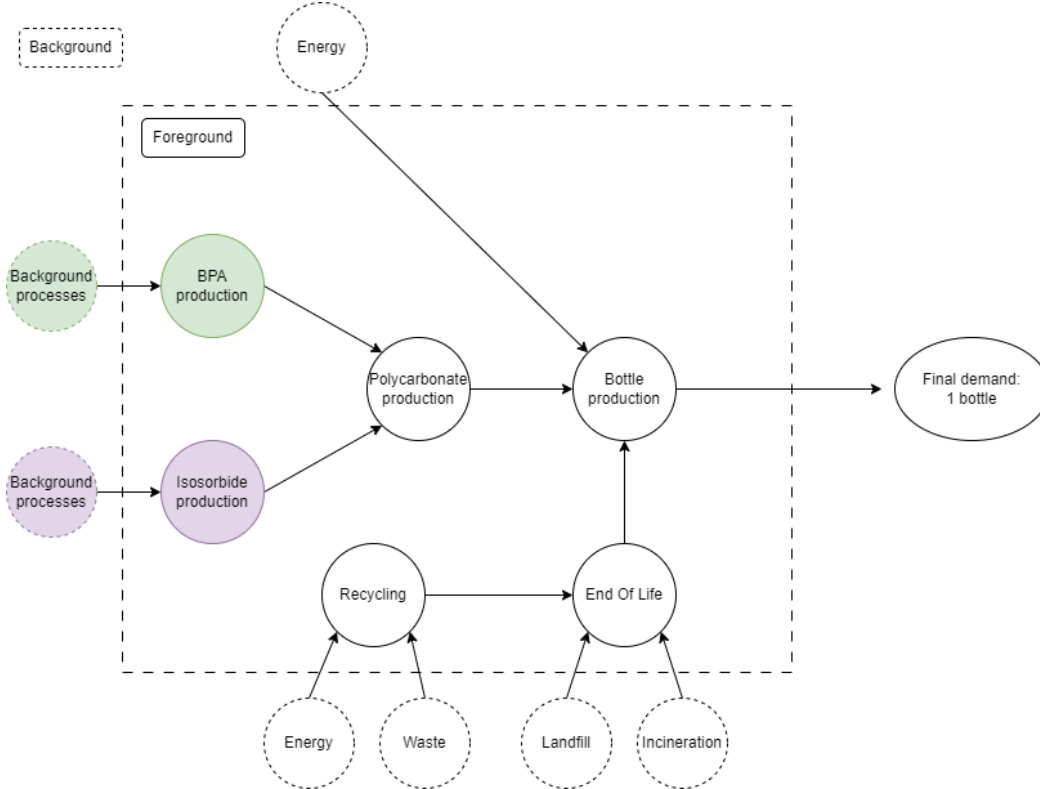


Figure 22 shows the foreground system modelled in quasaLCA. Highlighted are the individual unit processes for the production of BPA or Isosorbide, the production of polycarbonate from either, bottle production, and finally end-of-life collection and recycling (here shown as inflows to indicate the service provided rather than the waste flows). The use phase of the bottle, represented through a dishwashing process, was considered to be included, but left out of the analysis as we did not distinguish the number of washes over the service life between the two bottles.

The functional unit is the production of 1 bottle weighing 0.08 kg.

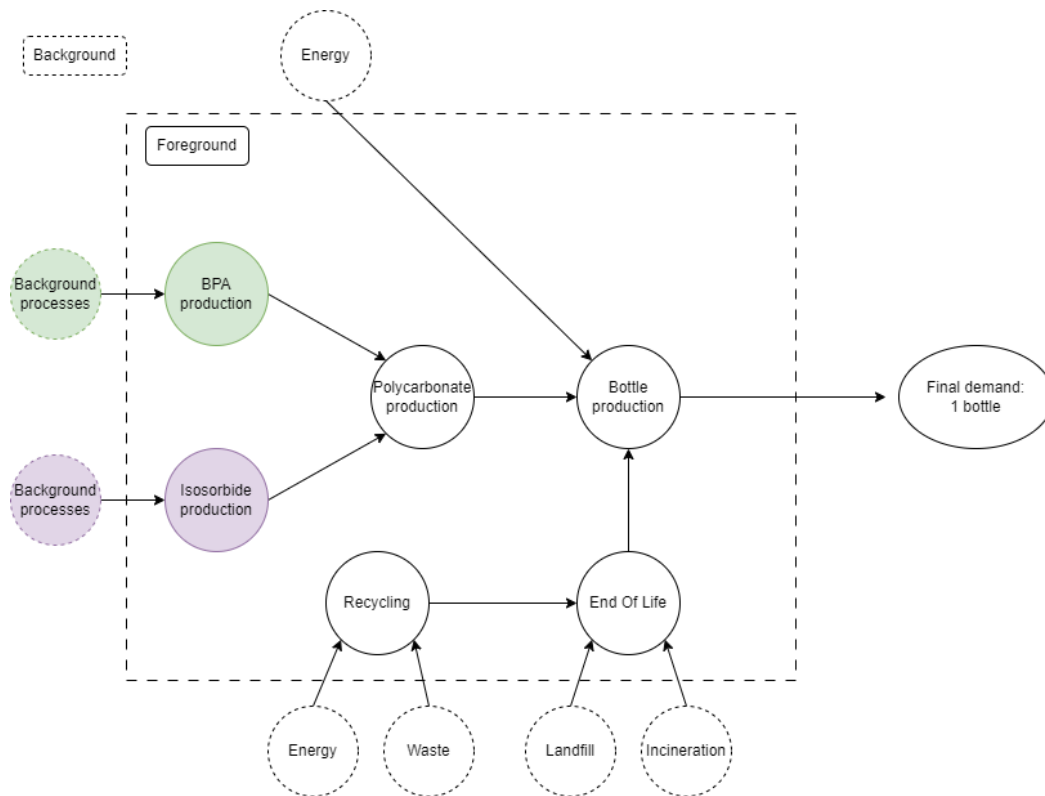


Figure 22: Flowsheet showing the processes modelled in the Life Cycle Inventory. Note that both BPA and Isosorbide routes are independent plastic bottle production routes but shown here in the same figure for brevity. Impacts associated with the use phase of the bottle are not considered in the model.

A standard Life Cycle Inventory is available for the production of BPA in ecoinvent. Here we copy the ecoinvent BPA background process (“bisphenol A production, powder”) and bring it explicitly in the foreground for the purpose of contribution analysis. The polycarbonate production process was modelled after Zhou et al. (2023), and the isosorbide unit process was modelled after de Souza et al. (2023).

Landfill and incineration processes were copied from ecoinvent (respectively the unit processes “treatment of waste plastic, mixture, sanitary landfill” and “treatment of waste plastic, mixture, municipal incineration with fly ash extraction”), and the energy use associated with recycling plastic bottles was taken from Jeswani et al. (2021). The following values were assumed for the ration between recycling, landfilling and incineration was used: 40 % recycling, 23% landfilling, and 37 % incineration.

4.5.2.2 Results

The baseline result values for the production of 1 bottle from either BPA or Isosorbide are presented in

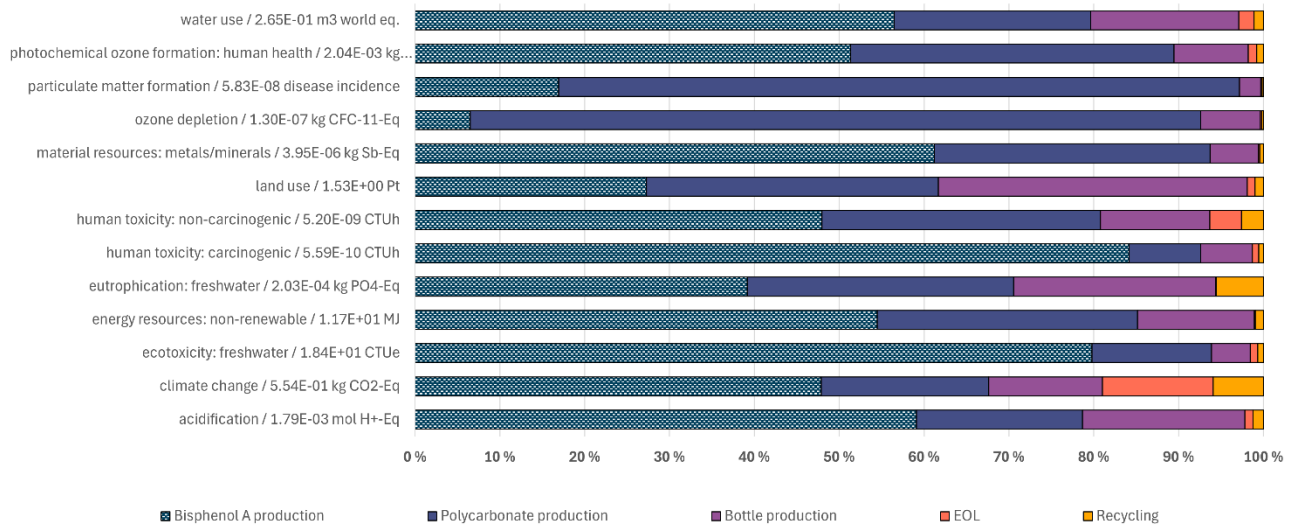


Figure 23 and Figure 24 respectively. The figures show advanced contribution analysis, i.e. the direct and indirect contributions to the environmental footprints of each of the modelled foreground processes. For all impact categories visualized, the isosorbide plastic bottle has a lower environmental footprint.

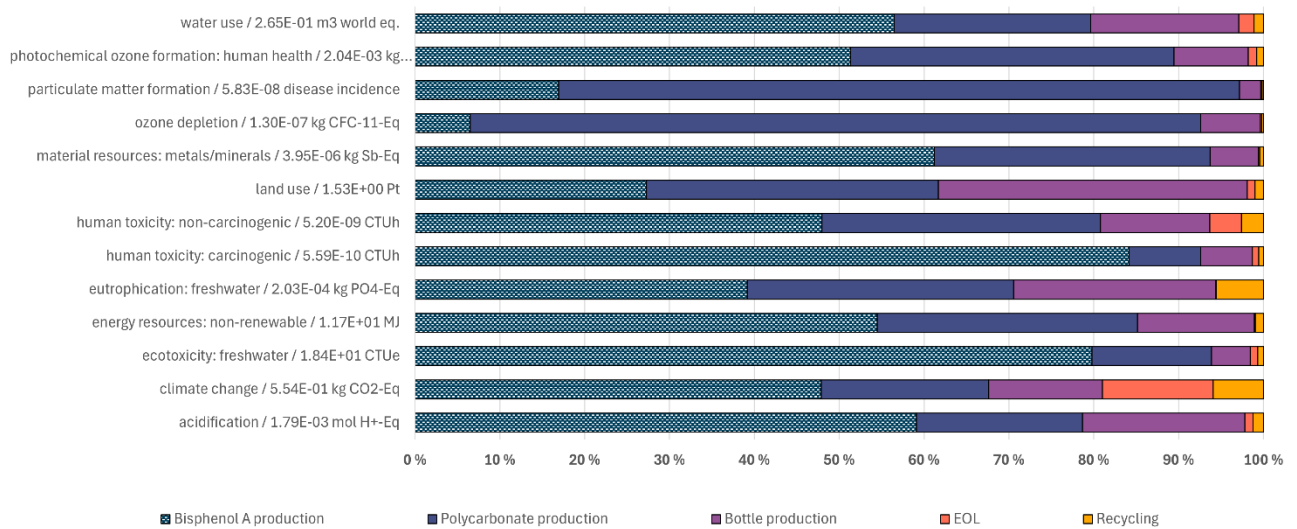


Figure 23: Advanced contribution analysis of the production and disposal of 1 plastic bottle from BPA.

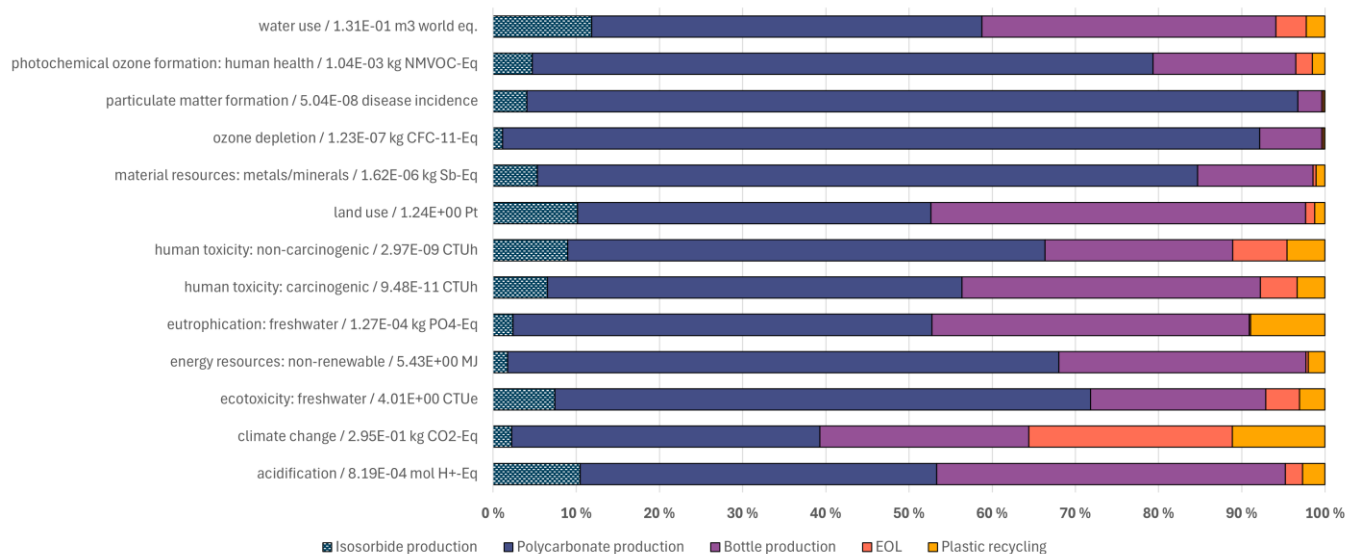


Figure 24: Advanced contribution analysis of the production and disposal of 1 plastic bottle made from isosorbide.

4.5.2.3 Discussion

LCA values were computed using NILUs in-house LCA calculator quasaLCA in combination with the ecoinvent v3 background database of unit processes. Here, we briefly discuss the suitability of the tool and LCA in general in an early phase chemical design process.

A first challenge is that the chemical process needs to be modelled in the form of a life cycle inventory. This is a tool independent problem, though there are LCA tools that come with a pre-installed library of unit processes which makes this process easier. QuasaLCA does not come with such a library, and we therefore were confined to the commercially available ecoinvent database, as well as LCIs published in literature. This provided coverage for some, but not all, of the required processes for our case study and this is a limitation. In addition, the quality of LCIs published in literature may differ, and often there is little metadata available, which may result in wrongful assumptions regarding geographic scope or functional unit. Also, LCIs may come as fully aggregated system processes, thus making it harder to adjust the upstream model and perform functions such as process, or environmental intervention, contribution analysis (not demonstrated in this working paper, but a function of quasaLCA). A comparison of results presented in sections 4.5.1 and 4.5.2 is out of scope of this document. A case study report is in preparation. However, the approach taken between the two LCA practitioner teams for this simple early stage screening LCA is already quite different.

Though not available with an extensive LCI library, quasaLCA does allow a level of customization due to its python codebase. It requires a good understanding of the mathematical concepts behind LCA and some skill in python programming using coding notebooks, but the flexibility and customization it offers is not available in other LCA software suites. The foreground Life Cycle Inventory model is input by the practitioner using a macro-enabled Excel spreadsheet. However, once an inventory is available, and key design parameters are identified, it can easily be embedded into apps that immediately give an LCA result based on user input and can be shared with non-LCA practitioners (provided license conditions associated with background databases such as ecoinvent are met). The LCA is transformed into a parameterized model capable of running scenarios. For example, while not demonstrated here, it is possible to run scenarios adding and changing transport distances, modifying background electricity mixes, or providing more detail on process-specific parameters such as material and energy efficiencies. This does require a certain level of expertise.

4.5.3 ProScale

4.5.3.1 Approach

An assessment of human toxicity and direct occupational exposure throughout the life cycle of polycarbonates produced using BPA, BPAP and isosorbide (ISB) as dihydroxy-functional monomers was performed using ProScale. A cradle-to-gate system was modelled, from raw materials processing (cradle) to polycarbonate powder production (gate). The data input for the ProScale assessment was the same as for the Gabi model (Table 92-Table 98). The case study was conducted for early stages of innovation: the system models were created as if processes for synthesizing BPA, BPAP, isosorbide, as well as polycarbonates synthesized from each of them, did not exist yet. Therefore, assumptions were needed to fill in data gaps.

4.5.3.2 Results and discussion

Below, the results of the ProScale assessment for BPA-, BPAP- and isosorbide-based polycarbonate with predicted and estimated input data are reported (Figure 25). ProScale provides a score for two exposure routes: inhalation and dermal exposure.

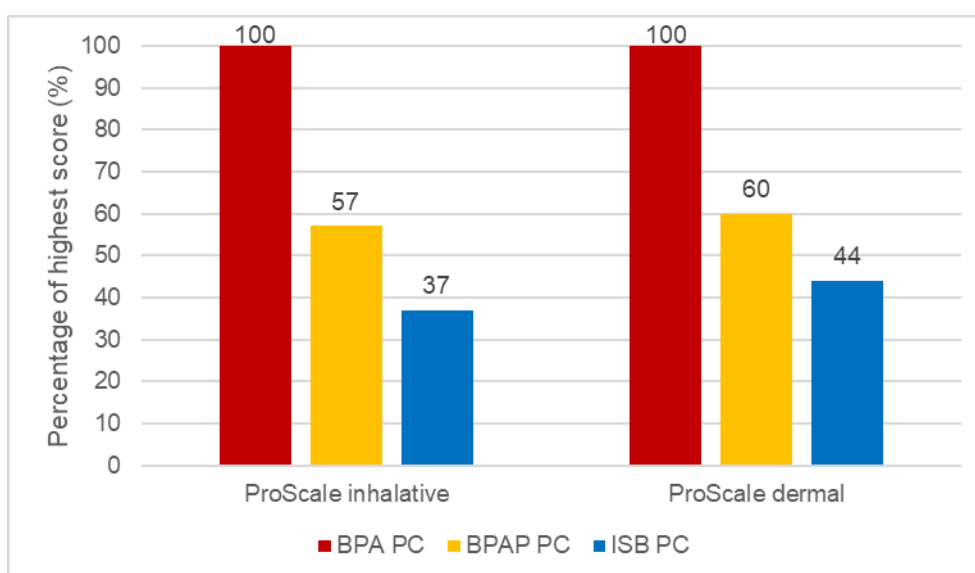


Figure 25: ProScale scores for the life cycle of BPA-, BPAP- and ISB-based polycarbonate with predicted and estimated input data for BPA, BPAP and isosorbide (ISB).

The results of a ProScale assessment correspond to a hazard- and exposure-based score giving quantitative information on direct-exposure related chemical risks (near-field human toxicity) to workers, professionals and consumers associated with products in a life cycle perspective (in this case, the assessment was limited to workers impact for cradle-to-gate systems, to be further elaborated in the forthcoming final case study report). When assessments of different products are done by using a consistent approach, the ProScale scores allow for a comparison of chemical risks in the life cycle of the products. For the approach to modelling applied in this case study, see section 4.5.3.1.

The ProScale scores of BPA-, BPAP- and ISB-based polycarbonate are reported in Figure 25 as percentage of the highest score. These results are only relative. It means that for the systems-as-studied, the total toxicity potential for the BPAP (cradle-to-gate) system, is 57 % of the system-as-studied for BPA, for the category ProScale inhalative. According to the obtained ProScale scores, BPA-based PC has the highest impact throughout its life cycle, both for inhalation and dermal exposure, whereas ISB-based polycarbonate has the lowest impact. It has to be noted that these are intermediate results, and the assessments were made to try applying the ProScale method to the selected products and life cycles in

early innovation stages. The results indicate that the approach is possible and provides useful information, but must not be considered a formal statement of the risks associated with the three products.

Since ProScale scores are an indication of toxicity potential throughout all processes in the life cycle of a product, it is relevant to analyse which processes contribute the most to the final scores. The final scores derive from the sum of individual ProScale of unit process (PSU) scores. The PSUs of all processes analysed in the life cycle of polycarbonates produced by using BPA, BPAP and ISB respectively are reported in Figure 26-Figure 28.

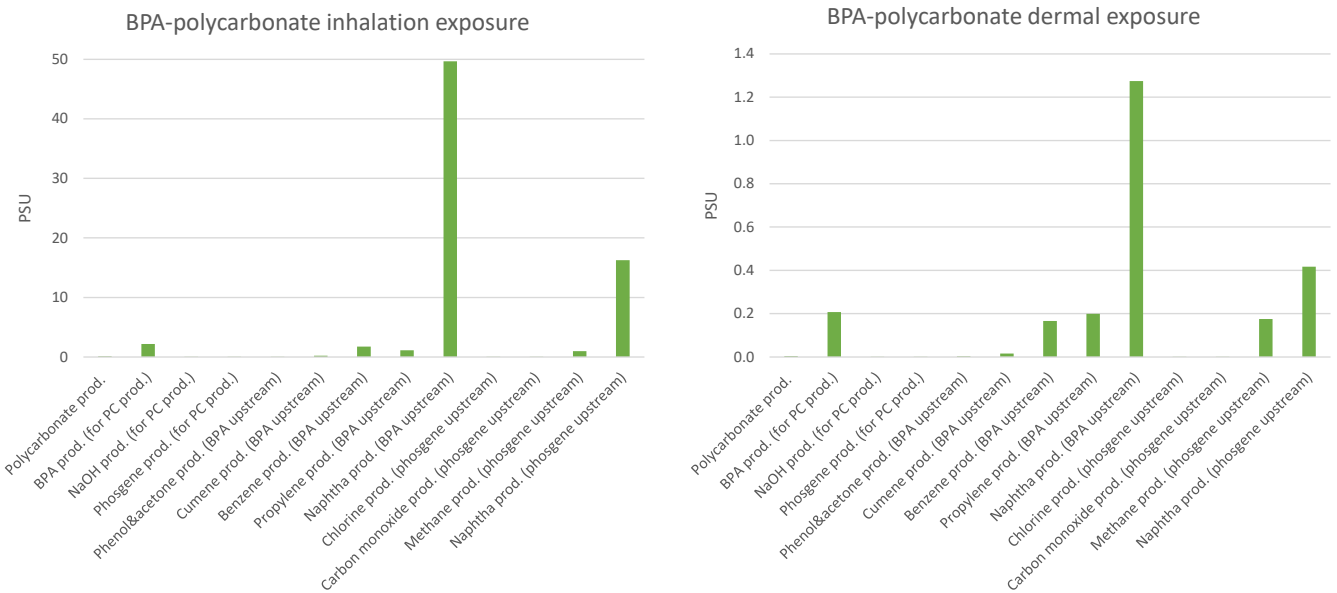


Figure 26 Contribution analysis for BPA-based polycarbonate, ProScale of unit process (PSU) scores for each process in the life cycle.

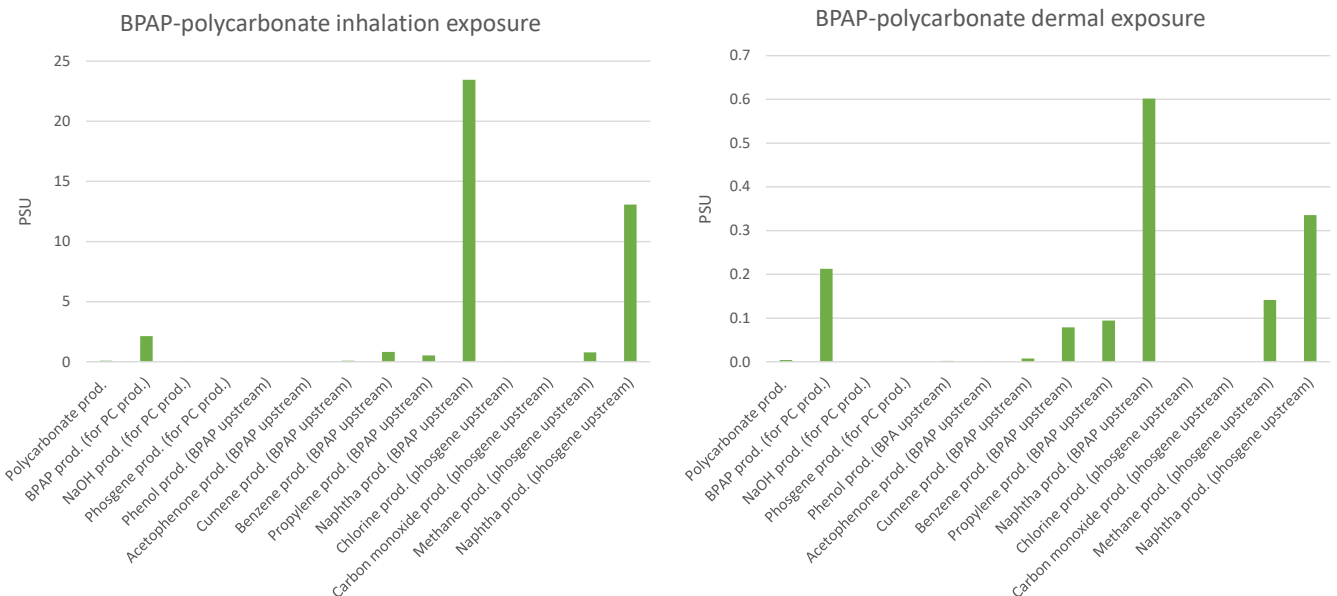


Figure 27 Contribution analysis for BPAP-based polycarbonate, ProScale of unit process (PSU) scores for each process in the life cycle.

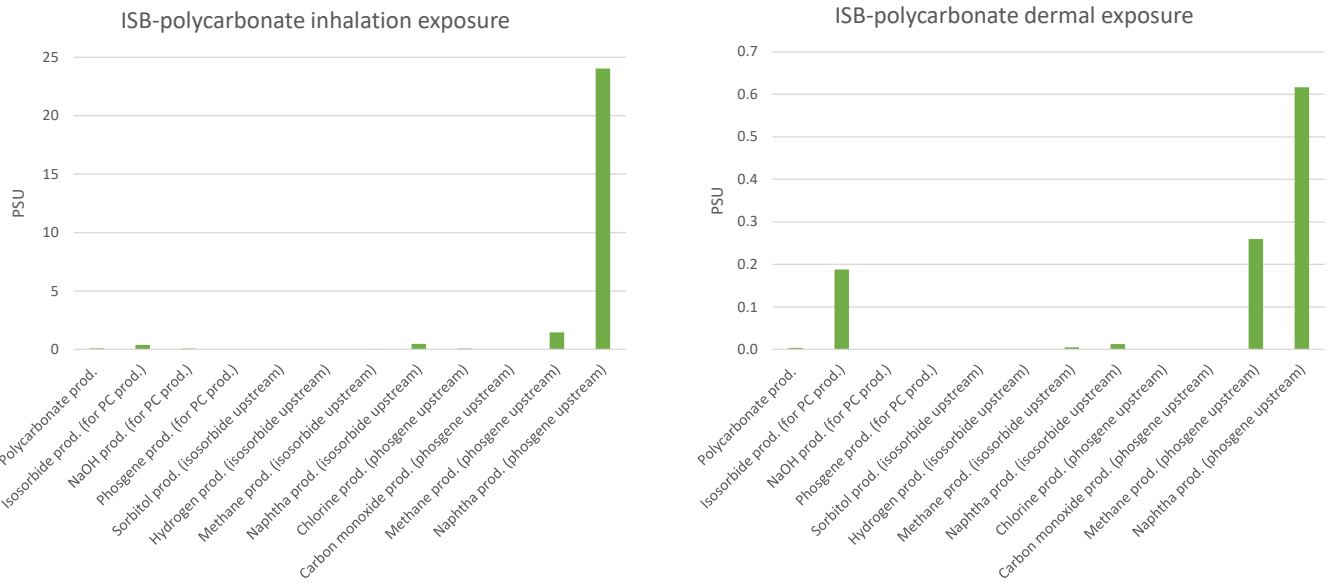


Figure 28 Contribution analysis for isosorbide-based polycarbonate, ProScale of unit process (PSU) scores for each process in the life cycle.

By using ProScale, the practitioner can investigate which processes are the major contributors to direct human toxicity impacts throughout the life cycle of a product. The results reported in Figure 26-Figure 28 highlight that upstream processes such as naphtha production are responsible for the highest impact in all product systems investigated.

4.5.3.3 Reference results

The results reported in section 4.5.3.2 can be compared with those obtained when reference system models were created by using all currently available data concerning BPA, BPAP and ISB production, as well as polycarbonate production using each of them as dihydroxy-functional monomer respectively (Figure 29).

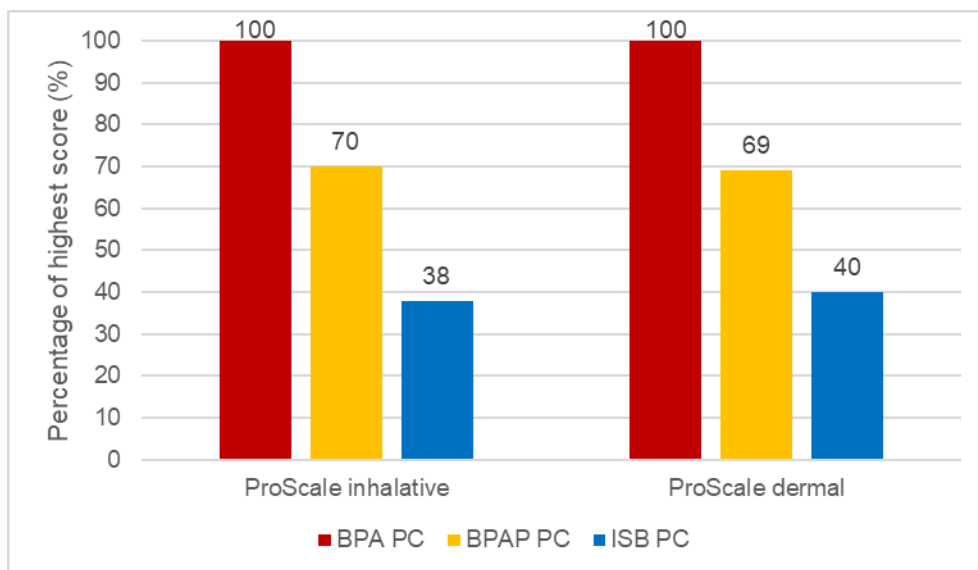


Figure 29: ProScale scores for the life cycle of BPA-, BPAP- and isosorbide-based polycarbonate modelled with all currently available data.

4.6 Step 5

There are several different tools and methodologies for assessing socio-economic impacts identified in the literature. Most of the methods use qualitative or semi-quantitative data to assess potential impacts on stakeholders affected by a product or process.

Following on from the brief literature review we tested the UNEP social life-cycle assessment (UNEP, 2021), using Bisphenol-A (BPA) as a case study.

The tool cannot be run with the data available. The following table (adapted from Stoycheva et al. (2022)) shows the categories from the UNEP S-LCA that have been identified as relevant to assessing the socio-economic impacts of chemicals at the stage of innovation for SSbD and the data that would be required to run the assessment. To avoid 'double counting' this assessment aimed to only consider social and economic aspects not assessed in previous stages of SSbD. An initial assessment could be run on the organisation producing the product, however for a more holistic and complete analysis all organisations involved in the attainment of raw materials, production, marketing, dispersal, use, and end of life of the product should be included.

Table 99: Data requirements to complete UNEP S-LCA

Category	Data needed
Workers	
Child labour	Whether organisation has links to child labour.
Fair salary	Wages paid by organisation, whether these meet the legal minimum wage in that country and whether they can be considered a living wage.
Working hours	The number of hours worked, whether this is in accordance with the International Labour Organisation (ILO) standards.
Forced labour	Verification that forced or compulsory labour is not used in the organisation.
Equal opportunities/discrimination	Assessment on the presence of discrimination within the organisation, defined as any distinction, exclusion or preference made on the basis of race, colour, sex, religion, political opinion, national extraction or social origin.
Workers' health and safety	Rate of health and safety incidents and the precautions in place to prevent them.
Local Communities	
Access to material resources.	Extent to which the organisation respect, work to protect, to provide or to improve community access to local material resources.
Delocalisation and migration	Whether organisations directly or indirectly dispossess individuals or groups of their land or resources.
Safe and healthy living conditions	Whether the operations of the organisation have any impact on the safety or health of local communities.
Respect of indigenous rights	Whether the organisation has any impact on indigenous peoples' rights to land, resources, cultural integrity, self-determination, and self-governance.
Local employment	The employment opportunities provided by the organisation to the local community.
Value chain actors	

Respect of intellectual property rights	Whether the organisation or product have any impact on intellectual property rights of other individuals and organisations.
Consumer	
Health and safety	The product or service provided by the organisation should perform their intended functions satisfactorily and not pose a risk to consumers health and safety.
End-of-life responsibility	Management efforts to address the social impacts of product or service end-of-life.
Society	
Prevention and mitigation of conflicts	Any current or future impacts an organisation could have on conflicts, positive or negative.
Contribution to economic development	The extent to which the organisation, product or service contributes to economic development of the country.
Corruption	Whether the organisation has implemented appropriate measures to prevent corruption or if there is any evidence that has been or is engaged in corruption.
Technological development	Whether the company participates in joint research and development for efficient and environmental sound technologies.

Other tools/methods and data requirements

Salieri et al. (2021) performed a socio-economic analysis (SEA) in combination with a Risk Assessment and Life Cycle Assessment when considering the safe and sustainable innovation of nanoparticles, namely a case study on Li-Ion batteries.

The SEA was performed by comparing a baseline scenario without the nanoparticles in vehicle batteries with the scenario of vehicles equipped with Li-Ion batteries containing nanoparticles. The analysis utilised data on CO₂-eq, SO₂-eq, NMVOC-eq, PM₁₀-eq, NO_x to assess impacts on climate change, acidification, photo-oxidant formation, PM formation, impacts due to NO_x formation along with human toxicity related to both cancer and non-cancer illnesses. To compare the two scenarios an 'Environmental Net Present Value' (Env-NPV) was calculated to include economic impacts as well as monetized environmental and health impacts.

A key issue with this approach is that the monetary value placed on each impact will affect the overall results. For example, the value given to a kg of CO₂ will impact the overall outcome of the assessment, this is a crucial consideration given the monetary value of these impacts is not static or unified making the assessment some-what subjective or at the very least variable.

In the socio-economic assessment performed via a spatial multi-criteria decision analysis by Purker et al. (2023) the data points considered were categorised into three areas of impact: society, economy, and technology. Within these, the impacts were labelled as being relevant to one or multiple of production/manufacture, use, and end of life. Finally, the impacts were split between three tiers that were considered sequentially. By categorising the impacts as such and maintaining these categories in the overall analysis of impacts it allowed a balance of the impacts to be maintained and helped to prevent overlooking the impacts on a specific area.

Pizzol et al. (2023) applied the approach to operationalise SSbD developed by the H2020 SUNSHINE project to two case studies: nano-enabled PFAS (Polyfluoroalkyl substances)-free anti-sticking coating for bakery moulds, and nano-drops of essential oil anchored to the surface of nano clays and encapsulated in a polymeric film. The approach is split into three tiers. Tier 1 was a self-assessment methodology to

assess environmental, safety, social, and economic impacts. This assessment takes place in the earliest stages of innovation, issues identified in tier 1 are then semi-quantitatively and quantitatively assessed later in the innovation process in tiers 2 and 3 respectively.

Tier 1 assessment is split into five categories: raw materials and resources, production of material, manufacturing of the product, use, and end of life. The social and economic considerations are listed in the table below.

As a comparison to the UNEP S-LCA methodology Table 100 shows the criteria used by Pizzol et al. (2023) taken from the H2020 SUNSHINE project for the social and economic aspects of the SSbD assessment.

Table 100: Criteria used by Pizzol et al. (2023) taken from H2020 SUNSHINE.

	Social Sustainability	Economic Sustainability
Raw materials and resources	Material resources access	Direct cost of raw materials
	Health and safety improvements	Direct cost of transport of far materials
	Traceability of raw materials	
	Absence of armed conflict	
	Raw materials coming from underdeveloped, developing, or third world countries	
Production of material	Health and safety improvement	Direct cost of waste disposal in production
	Local employment	Direct cost of maintenance for production
	Assessment of suppliers	Direct cost of installation (heating, lighting) for production
	Raw materials coming from underdeveloped, developing, or third world countries	Economic benefits of by-products/co-products
	Technological development, economic impact, education opportunities	Direct benefits of production
Manufacturing of the product	Local employment	Direct cost of waste disposal for manufacturing
	Assessment of suppliers	Direct cost of water treatment for manufacturing
	Raw materials coming from underdeveloped, developing, or third world countries	Direct cost of maintenance for manufacturing
	Technological development, economic impact, education opportunities	Direct cost of installation (heating, lighting) for manufacturing
		Direct benefits of product
Use	N/A	Direct benefits of product
End of life	End-of-life information	Direct costs of end-of-life

5. Lessons learned and next steps

Below we present an overview of the lessons learned during the execution of the case studies.

5.1 Step 1

5.1.1 Interpretation of QSAR results

QSAR based tools are easy to use- but the results are difficult to interpret

QSAR based tools are accessible computational tools that can be utilized by a broad range of individuals. Nevertheless, the interpretation of the results necessitates a certain level of expertise to ensure reliability, as QSAR tools can often yield conflicting values. This inconsistency is a recognized issue within the QSAR user community, and a way to deal with this can be seen in e.g. the Danish QSAR database. This will be subject to further work in PARC.

Within the framework of the case study, we have chosen to initiate the work with an interpretation guide on how to assess contradictive values given by a QSAR tool and how to handle conflicting results from different QSAR tools. This will be aligned with e.g. pieces of guidance from OECD and ECHA on the reliability assessment of QSAR type models.

We suggest that this is a work that should be handled as a separate task during year 3 of PARC and that it could involve several work packages. The results from such work would be valuable for several activities in addition to the work with the PARC toolbox and its wizard.

Identified gaps

During the Step 1 assessment of SSbD in early innovation, it was identified that there were notable gaps in the predictions of the required endpoints. More specifically, there are several endpoints, such as STOT-RE, STOT-SE, immunotoxicity and all the physical hazards, which couldn't be addressed by the available QSAR models in the PARC toolbox. This observation provides a valuable lesson on the applicability of the current version of the toolbox and facilitates the work on its further refinement and development.

5.2 Steps 2 and 3

5.2.1 Inventory and definition of input data

As it is important to make sure that the same values are used for the input data in the tools an inventory of input data will be compiled. By using the same input data we enable a comparison of the tools within the SSbD step.

Creation of a list of which SSbD endpoints are managed by the tools included in the case study. The list will visualize the coverage of endpoints and identify gaps, where there is a need for the development of new tools. During the work data gaps were identified, more specifically, no relevant QSAR models were identified that can predict the physical hazard endpoints.

Some tools also give predictions for endpoints, which are not included in the SSbD framework. These endpoints are also listed in the inventory. This allows us to identify any endpoints that might be interesting to include in the framework in the future.

5.2.2 Use of toxicological values – thresholds

In the context of risk assessment, the utilization of toxicological thresholds, such as DNEL and PNEC, is of utmost significance for deriving RCRs. Assessing the chemical risks in early innovation can be challenging due to the limited availability of toxicological data. To address the aforementioned challenge, it is critical to explore alternative techniques to generate the required data, such as in-silico methods for quantitative predictions (e.g., QSARs). However, this approach raises concerns about the accuracy and reliability of results. It is crucial that the assessor takes this fact into consideration during this stage and apply further testing moving towards the innovation process (Stages 3-4).

One such method is to employ read-across/grouping, in-vitro testing or further exploration of New Approach Methodologies (NAMs), such as omics and systems biology models, to predict the hazard potency of the chemical in question and the human relevant safe doses for the relevant exposure routes. Moreover, if further testing is needed, in vivo methods can be applied. Thus, the relevant toxicological thresholds will be further defined using a weight-of-evidence (WoE) approach. In the context of the current case study, an alternative approach to derive toxicological thresholds would be the application of read-across. This method will allow for the definition of the respective dose descriptors (e.g. NOAEL) and is considered one of the next steps in this work.

5.2.3 Assessing reliability of model outputs

Data quality is a measure of the reliability, validity, accuracy, completeness, and consistency of a data set. In all types of model calculations, the basic rule “data quality in \geq data quality out” applies. This implies that the quality of the model results can never exceed the quality of the data used as input to the model. Uncertainties in the input data can, however, add up to an increase of the uncertainty in the output data. A careful assessment of the data quality is thus crucial to understand how the model results can be used.

In the SSbD work, the quality of the data in the early innovation stage is often low, as knowledge about the new chemicals is limited. While models are available that will provide information about the physicochemical properties of the chemicals at a very early stage, this information may be unreliable. Using modeled physicochemical properties as input in further modelling tools for calculation of, for example human or environmental exposure or load, may accumulate the uncertainty in the resulting output. It is therefore crucial to assess the quality of the data and model results, and carefully consider how it may affect the conclusions based on this information. As new information is emerging in the later innovation stages, the data quality will likely increase, thus gradually increasing reliability of the model results.

This will by no means exclude the use of models in the early innovation stage of SSbD to assess the effects of the chemicals. If uncertainties are known and treated appropriately, model calculations can still provide very useful indications of the potential effects from new chemicals. Ideally, any use of models would be based on a thorough understanding of how uncertainty in all input and calculations steps influences the output data quality. This would, however, greatly limit the possibilities for model applications, and alternative approaches are needed to allow a wider use of the modeling tools available.

Three different approaches are suggested:

1. Careful use of uncertainty information provided by the model.
2. Understanding the sensitivity of the model to different input parameters.
3. Assessing a best- versus worst-case scenario.

As an example, a few tools have been selected for sensitivity analysis, amongst those are SimpleBox and ConsExpo.

5.3 Step 4

There is a need to predict process performance and emission characteristics in Step 4. Obviously, for a new chemical, produced in a new chemical process, there will be no existing LCI data available. But also for existing chemicals, there is a lack of LCIs of chemicals in general (Cespi et al., 2015, Hischer et al., 2005) and even major databases such as Ecoinvent only have a fraction of processes available detailing chemical production. Out of the nearly 20,000 unit processes in Ecoinvent, only 700 have a CAS number associated with them. This implies that LCA practitioners are required, in screening LCAs such as this one, to generate LCI and LCA results based on available information from other sources. However, the LCI information needed can be estimated (predicted) using engineering design principles (Jiménez-González et al., 2000, Piccinno et al., 2016). The quality of the result can vary widely (Parvatker and Eckelman, 2018, Meyer et al., 2021) and may be practitioner dependent. Commercial operators focusing on chemical process LCI data exist (carbon-minds.com, environmentalclarity.com), but we tried a different approach

In our work so far, we have applied default release factors for processes when simulating processes lacking data (Tables 96-98) as a means of exploring approaches to estimate LCIs for processes at low cost and effort. As a first rough estimate, it does work, but provides sometimes very overestimated numbers.

5.4 Step 5

Through this brief comparison (see 4.6) of the approaches taken to socio-economic assessments in literature and their data and information requirements it is clear there is huge diversity in the field. The results obtained for a socio-economic assessment will be affected by the methods chosen and tools utilised. Therefore, careful consideration into why a particular tool is being used and full transparency about the methods and data used is essential. Data availability is a common issue for many, if not all, of the approaches and this is particularly relevant for assessing the socio-economic impacts at the early stages of innovation due to the incomplete or unknown data. Making sure a socio-economic tool assessment is thorough while being realistic in its data requirements is a crucial balance to ensuring the validity of the outputs.

5.5 Timeline ahead

Work in task forces has been continued, resulting in a written report from each task force delivered by the end of April. The work with compiling all results from tool testing and reports from the task forces has been performed during May. Internal review by case study co-workers has been conducted in May. Complete and reviewed report is expected to be delivered during this year.

5.6 Next step: Questions to address in further work

5.6.1 Overall methodology

- 1) How do we best assess the reliability of the (model) predictions for the safety and sustainability parameters, and how do we integrate this into the SSbD assessment?

- 2) It is not sufficient to assume a linear economy perspective during the assessment of new substances, how do we incorporate this into the SSbD framework?
- 3) How do we fairly compare substances that exist on a different development level?
- 4) When producing new substances; should one particular use case be considered or a range of potential end-uses?

5.6.2 Sustainability assessments

- 1) In terms of production, how do we account for:
 - a. Multiple synthesis routes?¹⁹
 - b. Efficiency of production processes?²⁰
 - c. Substance emissions during production?
- 2) Methods for prospective LCA and LCA in general are currently missing in the toolbox, should this be discussed in the toolbox?

5.6.3 Risk or safety assessments

- 1) How do we best integrate different model predictions for the same endpoint?
- 2) How do we account for:
 - a. Substance related impurities?
 - b. Catalyst or additive related impurities?
 - c. Substance emissions during production?
- 3) Should we assume emission factors or model emission factors based on use scenarios?
- 4) How do we reverse engineer this case study description to fit all development stages for the three alternatives?
- 5) How to perform quantitative risk assessment in early innovation? How to define the required toxicological thresholds?

5.6.4 Added value for users

- 1) What kind of new information can be produced with the SSbD tools in real industry chemical substitution cases compared to the existing practices? What is the added value for industry?
- 2) What kind of resources are needed for using the tools or the information produced by the tools?
- 3) Is the information objective (not dependent on the expertise of the tool user) and relevant for decision making?

¹⁹ We reiterate that this is a fictitious case implemented through a so-called dry run approach. In a real case, since it is at innovation stage, this would also be considered as a core part for the assessment, and scenarios are key to understand the different synthesis routes also to have a process redesign.

²⁰ Same as ²¹

6. Other uptake

6.1. Connecting SSbD Toolbox users

In the course of 2023 there has been a substantial outreach to both companies and sector organizations, and other stakeholders. The goal of the outreach was to on the one hand inform them about the SSbD activities presently going on in PARC and to initialize contact for follow-up discussion on existing industry practices on SSbD.

Through in-depth interviews and focus groups with companies involved in chemical and product development, we addressed the following overarching questions: a) What is the current link between innovation, safety and sustainability in chemical and product innovation? b) What does the state of the art within companies teach us about the further operationalization of SSbD? These overarching questions translate to the following focus areas that were explored in the interaction with companies:

- **The chemical/material innovation process**
 - How does the innovation on development of new chemicals and materials work in the company? What steps are being taken? Who are involved? How is it decided?
- **Current Safety and sustainability thinking in the innovation process**
 - How are safety and sustainability now included in the innovation process? Which models and data are used? How does the company come to a decision and take the next step?
- **Response to European developments in safe and sustainable innovation**
 - How are recent developments in safety and sustainability thinking incorporated into the innovation process? What is needed in terms of knowledge, data and tools?
- **Enabling Environment**
 - What are the policy and other drivers of innovation in the company? What is needed in terms of governance mechanisms, business models and educational needs?

Interview and focus group approach

Our approach was as follows.

- Chemical companies producing novel chemicals (*producers* in REACH terminology) and developing chemical based products (*formulators* in REACH terminology) were chosen, with a slight preference for producers given the focus of SSbD. Given the substantial time commitment required from industry, the choice of companies was not random.
- Companies engaging with the SSbD topic were invited to an initial discussion to explore their interest in engaging with us, and leaflets developed on the toolbox and the interviews were shared. The initial discussion explored the purpose of the interviews, the interest and fit of the companies for the interviews, and any concern.
- As SSbD involves multiple expertise, we sought to put together a team of experts as far as possible from both the company and interview team.
- As exploration of innovation within companies entailed that potentially sensitive information, we proposed to prepare an interview report based on an MS Teams recording of the interview, which would be shared with the company and finalized together.
- Company names and identifying details have been anonymized in the company reports.
- The interview reports were formally authorized by the companies.

We interviewed eight companies for approximately three hours each. Following an introduction of the company and PARC, the interaction followed the questions stated above, with a lot of discussion and clarification. Interviewers did not have a social science background, indeed the exploration required in

depth knowledge of one or more aspects of SSbD. In order to follow best practices of social science, the interviewers were trained by social scientists on best practices of interview methodology. Additional interviews on specialized topics (e.g. New Approach Methodologies, Cheminformatic Approaches) were scheduled when the company had substantial expertise in these areas. The interview reports are now being finalized and will be reported in an upcoming milestone. The interview reports will be analyzed further and will form the basis of a scientific article. Preliminary results and conclusions draw the following general conclusions from the company interviews/focus group. Stage gate is commonly used way of organizing the innovation process. While the stage gate itself is structured, innovation itself is nonlinear and highly iterative. Given the diversity of expertise and deep dives on tradeoffs in stage gate meetings, one respondent mentioned the stage gate process itself as the key source of learning on SSbD. The starting point of innovation i.e. novel chemical development, produce development, process optimization and the companies vantage point in the value chain plays a decisive role in the type of SSbD approaches employed decision making in stage gate meetings is a team effort, and final decision is driven not by any one criteria but rather by strategic considerations (e.g. corporate and sustainability strategy, profits, customer needs, reputational risk). A key goal is to balance functionality requirements with safety and sustainability aspects, within the framework of economic feasibility. SSbD is company and industry specific. For example, when the innovation is process based, hazard assessment involves standard ingredients and are routine whereas process design-based sustainability assessment plays a substantial role. Another example is that some industries require expensive infrastructure and specific value chains and may not be able to change much. In some cases, safety and sustainability tools may not be applicable (e.g. QSARS do not exist for metals and inorganics). Safety and sustainability practices range widely from specific tools to certification schemes. SSbD implementation is a team effort that requires both generalist and specific expertise. A few generalized insights can be drawn on the current link between innovation, safety and sustainability. Innovation here comprises of an exploratory phase, development phase and a market phase.

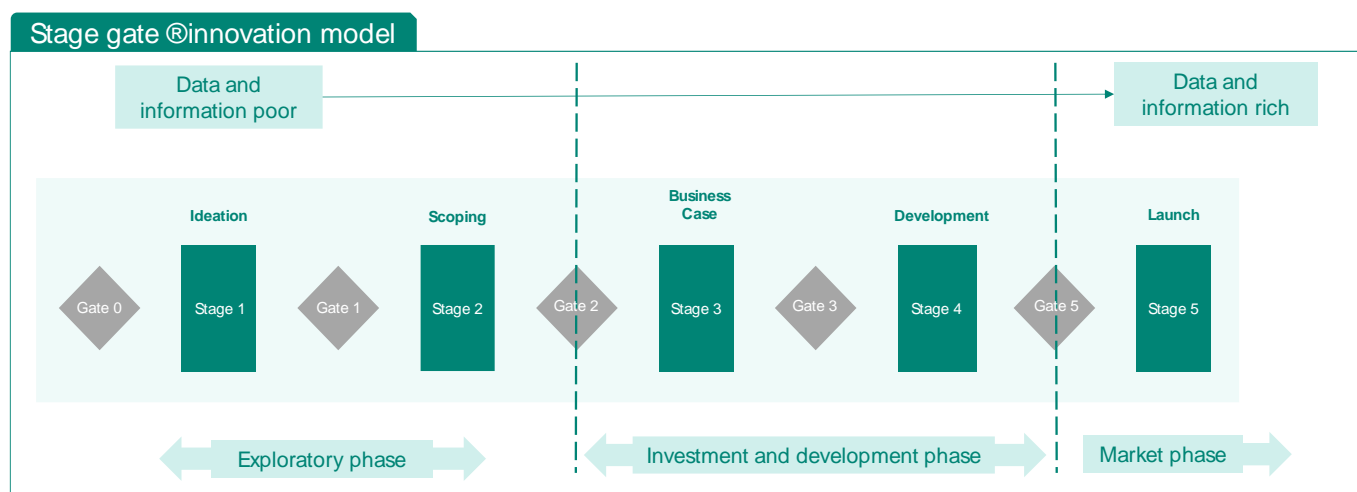


Figure 30: Stage gate approach involving three different development phases

The exploratory phase is characterized by limited time and money and exploration of several options. Application and desired functionality are known at this stage. The key goals in this phase is to establish the proof of principle (“Does it work?”) and proof of benefit (“Does it serve customer needs with feasible economics?”). This phase calls for quick analysis of numerous options in order to “Fail early, Fail cheap”. Typical safety assessment involves screening approaches in silico tools based on chemical similarity principle and control banding, checklists and literature, as well as expert judgement. Sustainability assessment has a limited role in the exploratory phase, and heuristic approaches based are typically used. The exception here is in process innovation, where detailed process models and measurements lend themselves to prospective/ ex ante Life Cycle Assessment approaches. The company sustainability strategy influences the choice of impacts considered. In line with the Portfolio Sustainability Assessment concept, sustainability is typically at the portfolio level and continues to remain so unless clients or customers request product level assessments. The investment and development phase allocates dedicated resources to develop a promising concept. Typical safety assessment entails the use of

application relevant assessments like NAMs. Impending regulatory requirements also play a role in the type of safety approaches used. Sustainability assessments may involve a screening LCA. Mapping the lifecycle and collaboration with value chain actors to perform a cradle to grave analysis commonly occurs at this stage. Most companies are involved in industry wide initiatives to reduce their greenhouse gas emissions, so climate chain related impacts are usually considered. The market phase is characterized by a proven functionality and a clear market perspective. Safety assessments now focus heavily on regulation requirements. Detailed sustainability assessments at the portfolio level are typically performed, and in some cases a Product Environmental Footprint may be done. The concept of planetary boundaries is considered interesting but too immature to apply currently.

6.2. Mistra SafeChem collaboration

In cooperation with Mistra SafeChem (MSC) three MSC case studies have been chosen for further testing of the PARC toolbox:

1. Textile recycling: Optimizing sustainability

In this case study cotton-based textiles are converted into cellulose nanocrystals (CNC) using acid hydrolysis in a water-based system. The development of a new milder processing route has been investigated, where citric acid was used for acid hydrolysis. The aim is to develop safer process routes and reagent recycling for improved environmental performance compared to other textile recycling routes. In the case study together with PARC the focus will be on aryl amines and skin sensitization. One of the tasks will be to identify models for skin sensitization available in PARC toolbox that are not incorporated in the Mistra SafeChem approach. The models have been run by PARC partner EMPA and results sent to MSC partners for analysis.

2. Safer and more sustainable by design in discovery chemistry

In this case study, a biocatalytic pipeline for sustainable and safe discovery chemistry is developed and validated. Within the MSC case study the ECOSAR tool was employed to forecast potential ecotoxicity hazards. However, there is an interest in utilizing additional tools for the same purpose and comparing the outcomes. The tools under consideration are primarily those used for assessing ecotoxicity hazards. The PARC partner, AUTH, has executed tests using mainly the VEGA model and partially the Danish QSAR Database. This comparative approach could potentially provide a more comprehensive understanding of the ecotoxicity hazards.

3. Cyclosiloxanes and silicones in cosmetics

In this MSC case study the environmental effects of silicones are studied and when necessary, suitable substitutes or alternative processes are identified or developed. This entails hazard and risk-based prioritization followed by alternatives assessment for substitution to minimize risks to humans and the environment from siloxanes or other chemicals providing similar function in cosmetics. The aim is to achieve a substitution with a systems perspective assuring not only increased safety but also improved environmental performance of the alternatives.

INTEGRA and ProScale were identified as relevant PARC tools for the case study for testing the reference substance D5 and 3-4 alternative compounds. The PARC partner, AUTH, has executed tests using INTEGRA and PARC partner IVL have run the tool ProScale. Results have been reported to MSC.

6.3. Outreach to other projects

During year 1 of the project, a compilation was made of then known case studies that could be interesting for PARC to collaborate with. The plan is to use a number of criteria to select the most suitable case studies for a PARC collaboration.

In spring 2024, work has begun on mapping SSbD-related research projects. The purpose is to see synergies and collaboration opportunities, and to investigate the possibility of tools developed within the framework of the projects, could be included in PARC's toolbox. See Annex for a list of SSbD related research projects.

6.3.1 Linking new SSbD projects to the PARC toolbox

Within Task 8.1, a new activity has been initiated focusing on establishing links with the new EU SSbD projects funded under HORIZON-CL4-RESILIENCE-01. This activity aims to create an interlinkage among the projects and establish a placeholder for newly developed tools in the PARC SSbD toolbox. Moreover, it could facilitate the current approaches and challenges of SSbD, by exchanging valuable insights and knowledge. In order to implement this activity, a five-step approach has been structured, including the following:

- Mapping of the projects: a compilation of a list of the projects, including their objectives, coordinators and partners
- Communication: communication will be established through official channels from the EC
- Identification of innovation actions: identification of the innovation actions of each project and the relevance with PARC
- Mapping of the activity needs of Task 8.1: identification and mapping of the information needs from the new SSbD projects (e.g., tools, platforms, education material, data)
- Creating links – engagement of the PARC 8.1 partners: links between the 8.1 partners and each project will be created based on their expertise, via SYNnet (WP3).

At present, a mapping of the 12 new projects has been carried out, as shown in the figure below (Figure 31). Moreover, a list including their objectives and coordinators has been compiled. The next step is to initiate communication with the projects via the EC, which is currently in progress.

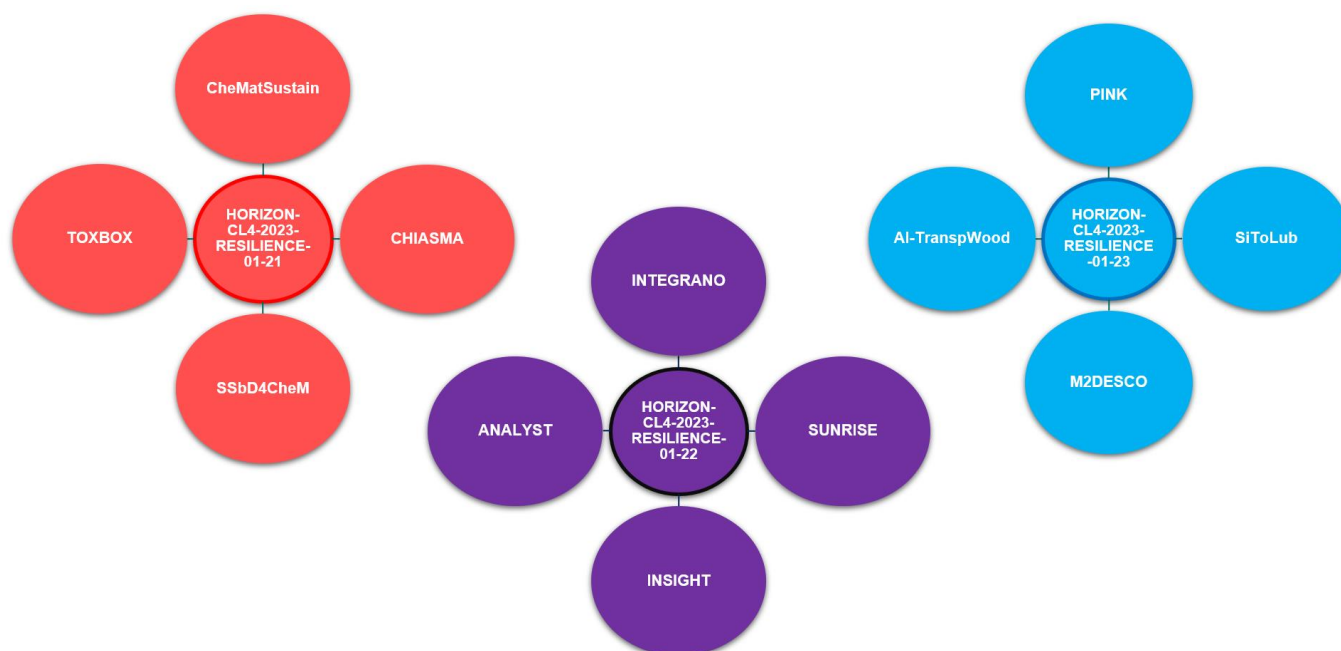


Figure 31: Mapping of the new SSbD projects under HORIZON-CL4-RESILIENCE-01

6.4. Technical expert group

SSbD is an approach that is still under development both from the policy side as well as all aspects focused on making SSbD operational. Whereas PARC has a strong focus on development of the toolbox and preparing an education and knowledge sharing platform, the IRISS – International SSbD Network project has a strong focus on bringing value chains together on an EU scale discussing and preparing all aspects of making SSbD operational. The main goal of the IRISS project is the establishment of connections and the transformation of the SSbD community, both at European and global level, with a focus on adopting a lifecycle approach²¹.

To enable an optimal science-policy interface a monthly regular exchange was set-up between DG RTD, DG JRC, IRISS and PARC. The focus of this technical expert group is:

- Exchange information on SSbD relevant developments
- Share information and results stimulating improved development of SSbD
- Investigate potential areas of cooperation
- Discuss SSbD related issues and ways to move forward.

6.5. Utility of SSbD tools in the decision-making process of chemical substitution

A case study with industry partners was initiated to evaluate the utility of the SSbD tools from an industry perspective. Industry partners who are in the process of substituting a harmful chemical, or have recently done so, were recruited through the Chemical Industry Federation of Finland. So far, three prospective

²¹ <https://iriss-ssbd.eu/iriss>

cases have been identified and tool testing was initiated with one industry partner. The case study will include testing selected SSbD tools covering steps 1-4 from the JRC SSbD framework (FIOH, SYKE, others?) and MCDA analysis (FIOH). A dialogue with the industry partners will be maintained during the SSbD tool testing to understand how the tool output should be processed or presented for optimal utility. A workshop will be held with each partner concentrating on refining the MCDA application and collecting feedback for the utility of each tool.

7. Conclusions

Both the building of the toolbox and testing of the tools are currently still ongoing, and will continue for the upcoming period, but some important conclusions can already be drawn in this intermediate stage.

The complexity of SSbD lies in the breadth of assessment types that is required to cover the whole framework.

The toolbox and the tools contained

- With the current set of tools in the toolbox we were able to cover a substantial amount of the endpoints and topics from the EU SSbD framework. As such the toolbox development, which is still in its early stage, is already a major step in the right direction. Advanced models are available for RA as well as for LCA. These are important as basis for validation of models vs measurements, but simplified versions/simpler models are needed for early design phases
- The toolbox now consists of computational tools, which are an important basis for early innovation stage testing. QSARs play a key role at the early innovation stages, and are critical for Step 1. In the future additional tools will need to be added that include e.g. in-vitro NAMs, read across approaches, AOPs, early sustainability assessment methods (prospective LCA), heuristic approaches etc. Moreover, the development of reliable models for predicting toxicity of alternatives structures is critical for go or no go at next stages.
- We have identified a number of gaps in the toolbox, i.e. a number of endpoints for which no computational tool is presently available. Additional work is needed to assess whether tool development in these cases is both necessary and possible.
- Computational tools require a set of input data. Many different tools also mean many different input data sets, varying quality of data, uncertainty of data, non-uniformity of data etc. That is, there are substantial issues and questions surrounding the use of these tools in combination with data, which require time, expertise and (financial) capacity to resolve.
- Different models have different strengths and weaknesses, and the predictive power depends to a large extent on the specific substance and hazard endpoint in question. Ways to combine the different models and model predictions taking into account the specific applicability domain will be subject to further exploration in PARC.
- The SSbD framework consists of different steps. Alignment of these steps – i.e. assessed in a methodological similar way – is needed. Interpreting the output of the tools, combining output from different tools, assessing the overall result for the various safety and sustainability endpoints result in a complicated web of outputs which needs substantial future work to untangle. Moreover, the development of an MCDA framework within the context PARC toolbox is of significant importance. This development will aid the decision-making and communication, as well as the integration of RA and LCA.
- Chemical space is huge resulting in many scoping issues for the toolbox and additionally there are many scoping issues surrounding the policy choices (e.g. how to deal with circular economy) that need to be resolved. Our current efforts are important and will help to get a good insight in these scoping issues and to prepare for a way forward.

Working process

- Considering the overall complexity, the many uncertainties and the very limited resources we have been able to put together an excellent testing team and strategy and have been able to make substantial progress.

- Testing the toolbox within the context of an SSbD framework that is still in development is demanding. As many things are still uncertain and unclear finding a mutually acceptable way forward requires substantial effort and consequently substantial manpower.
- SSbD is a holistic approach and requires input from various and different fields of expertise. At this moment in time there is no generally accepted vocabulary and terminology. This again requires substantial joint effort to come to a common understanding of what needs to be done.
- Resources and dedicated manpower are limited, already now but also in the tasks ahead. Additional funds are both necessary and welcomed.

Expertise

- At this moment the toolbox consists of computational tools for the various elements of the SSbD assessment. Each specific tool requires a specific understanding of, amongst others the required input data, output results, adjustable parameters, interpretation and assessment of the results etc. That is, for each tool a high level of expertise is needed to run the tool and interpret the results. In early phases of innovation qualitative expert judgement, semi-quantitative models, and computational models, all have a role to play. Interestingly, this is a common denominator for all SSbD steps. And predictive models are needed, and are also available, for all steps. For a specific step or stage in the SSbD assessment more than one tool is commonly available. Different tools might give conflicting results. Again this requires in-depth knowledge of both the tools and the field of application to assess and resolve these issues. Generally, the assessment of the tool output in relation to e.g. a specific safety or sustainability question is not straightforward. The context of SSbD (especially early stages) adds an additional layer of complexity and requires a specific set of expertise.

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Appendix

Case study Reporting template

Tool name / Tool version / Partner acronym

1. Structures and applications tested

2. Description of road to input data

If the tool cannot be run with the information given for each substance (structure and application), describe what you need to do to be able to run the tool. What additional input data are necessary if any, what tools/methods are needed to get those data, which are the steps to generate the data?

3. Results

List the values of input data and output endpoints for each substance (and each application, if relevant for the tool). If relevant, report the reliability of the results. The results can be reported in a separate Excel file if preferred.

4. Discussion of results

5. Innovation stage, SSbD step

If possible, suggest in which innovation stage and SSbD step the tool is most properly used.

6. Applicability domain

If relevant, describe the applicability domain of the model.

7. Reference values

Before collecting reference/experimental values, check whether the values are already present in the file [PARC 8.1.3 BPA Case study result.xlsx](#).

8. Additional comments

Reference data

Table 101: Input data for Steps 2 and 3 (late innovation)

		BPA	BPAP	Isosorbide
Source	ECHA	https://echa.europa.eu/el/registration-dossier/-/registered-dossier/15752	https://echa.europa.eu/el/registration-dossier/-/registered-dossier/9115/1/1	https://echa.europa.eu/el/registration-dossier/-/registered-dossier/5661/1/1
General	EC number	201-245-8	433-130-5	211-492-3
	CAS number	80-05-7	1571-75-1	652-67-5
Physicochemical properties	Physical state at 20°C and 1013 hPa	solid	solid	solid
	Molecular weight	228.28	290.36	146.14
	Melting point at 101 325 Pa (°C)	155	172	61.3
	Vapor pressure (Pa) *	4.12E-07	2.69E-06	2.09E-03
	Partition coefficient (Log Kow)	3.4	2.3	-1.39
	Water solubility (mg/L)	300	>9.04	2.312
Environmental fate properties	Henry's law constant (in Pa m ³ /mol)	3.12E-07	No data	No data
	degradation constant for soil (1/hr)*	2.60E-07	3.50E-04	9.6E-04
	degradation constant for water (1/hr)*	5.28E-07	7.70E-04	1.92E-03
	degradation constant for sediment (1/hr)*	2.70E-08	8.56E-05	2.13E-04
	degradation constant for air (1/hr)*	3.80E-05	0.23	0.099
	solids-water partition coefficient (1/hr)	30.93	442.55	0.013
	Log Koc	2.8-2.97	1.84	No data

*US CompTox Chemical Dashboard (BPAP)

*EPISuite

Table 102: Input data for Steps 2 and 3 (early innovation)

		BPA	BPAP	Isosorbide	Source
General	SMILES Code	<chem>CC(C)(C1=CC=C(O)C=C1)C1=CC=C(O)C=C1</chem>	<chem>CC(C1=CC=CC=C1)(C1=CC=C(O)C=C1)C1=CC=C(O)C=C1</chem>	<chem>C1C(C2C(O1)C(CO2)O)O</chem>	
	EC number	201-245-8	433-130-5	211-492-3	
	CAS number	80-05-7	1571-75-1	652-67-5	
Physicochemical properties	Molecular weight	228.31	290.36	146.14	VEGA
	Melting point at 101 325 Pa (°C)	131.76	182.2	60.53	EPISUITE
	Vapor pressure (Pa)	2.59E-04	1.31E-04	8.90E-03	VEGA
	Partition coefficient (Log Kow)	3.32	5.38	-2.27	VEGA

	Water solubility (mg/L)	172.7	3.758	4.71E+05	EPISUITE
	Henry's law constant (in Pa m³/mol)	9.28E-07	5.64E-08	0.00001269	EPISUITE
Environmental fate properties	degradation constant for soil (1/hr)	3.50E-04	3.50E-04	9.6E-04	EPISUITE
	degradation constant for water (1/hr)	7.70E-04	7.70E-04	1.92E-03	EPISUITE
	degradation constant for sediment (1/hr)	8.56E-05	8.56E-05	2.13E-04	EPISUITE
	degradation constant for air (1/hr)	0.23	0.23	0.099	EPISUITE
	solids-water partition coefficient (1/hr)	30.93	442.55	0.013	EPISUITE
	Log Koc	3.095	3.947	-0.582	EPISUITE

Table 103: Reference values in early and late innovation stages

Reference value	BPA DNELs		BPAP DNELs		Isosorbide DNELs	
	Early Innovation	Late Innovation	Early Innovation	Late Innovation	Early Innovation	Late Innovation
<i>Worker Inhalation (mg/m³)</i>	0.138	2	0.19		12.88	165.23
<i>Worker Dermal (mg/kg bw day)</i>	0.039	0.066	0.055		3.65	697.29
<i>Consumer Inhalation (mg/m³)</i>	0.25	1	0.35		23.19	297.5
Reference value	TDIs					
Innovation stages	Early Innovation	Late Innovation	Early Innovation	Late Innovation	Early Innovation	Late Innovation
<i>(mg/kg)</i>	0.043	0.0000002	0.06		3.91	33.47
Reference value	PNECs					
Innovation stages	Early Innovation	Late Innovation	Early Innovation	Late Innovation	Early Innovation	Late Innovation
<i>Freshwater (mg/l)</i>	0.027	0.023	0.011		75.47	0.107
<i>Marine Water (mg/l)</i>	0.0027	0.019	0.001		7.5	0.011
<i>Freshwater sediment (mg/kg sediment dw)</i>	0.6405	1.2	2.121		59.49	0.4
<i>Marine water sediment (mg/kg sediment dw)</i>	0.064	0.24	0.213		5.95	0.04
<i>Soil (mg/kg soil dw)</i>	0.508	3.7	1.719		9.22	0.016

Table 104: PROCs used in ECETOC TRA

Contributing scenarios	PROC number	PROC name
<i>Manufacture BPA</i>	PROC2	Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions
<i>Manufacture BPA</i>	PROC8b	Transfer of substance or mixture (charging and discharging) at dedicated facilities
<i>Manufacture BPA</i>	PROC9	Transfer of substance or mixture into small containers (dedicated filling line, including weighing)
<i>Manufacture BPAP</i>	PROC2	Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions
<i>Manufacture BPAP</i>	PROC8b	Transfer of substance or mixture (charging and discharging) at dedicated facilities ²⁶
<i>Manufacture BPAP</i>	PROC9	Transfer of substance or mixture into small containers (dedicated filling line, including weighing)
<i>Manufacture Isosorbide</i>	PROC3	Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions
<i>Manufacture Isosorbide</i>	PROC8b	Transfer of substance or mixture (charging and discharging) at dedicated facilities
<i>Manufacture Isosorbide</i>	PROC4	Chemical production where opportunity for exposure arises
<i>Polycarbonate production</i>	PROC1	Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions
<i>Polycarbonate production</i>	PROC2	Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions
<i>Polycarbonate production</i>	PROC8b	Transfer of substance or mixture (charging and discharging) at dedicated facilities
<i>Polycarbonate bottle production</i>	PROC9	Transfer of substance or mixture into small containers (dedicated filling line, including weighing)
<i>Polycarbonate bottle production</i>	PROC8b	Transfer of substance or mixture (charging and discharging) at dedicated facilities
<i>Polycarbonate bottle production</i>	PROC14	Tabletting, compression, extrusion, pelletisation, granulation
<i>Polycarbonate bottle production</i>	PROC6	Calendering operations
<i>Polycarbonate bottle production</i>	PROC10	Roller application or brushing
<i>Polycarbonate bottle production</i>	PROC15	Use as laboratory reagent
<i>Epoxy Resin production</i>	PROC1	Chemical production or refinery in closed process without likelihood of

<i>Epoxy Resin production</i>	PROC2	exposure or processes with equivalent containment conditions Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions
<i>Epoxy Resin production</i>	PROC3	Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions
<i>Epoxy Resin production</i>	PROC4	Chemical production where opportunity for exposure arises
<i>Epoxy Resin production</i>	PROC5	Mixing or blending in batch processes
<i>Epoxy Resin production</i>	PROC8b	Transfer of substance or mixture (charging and discharging) at dedicated facilities
<i>Epoxy Resin production</i>	PROC8b	Transfer of substance or mixture (charging and discharging) at dedicated facilities
<i>Epoxy Resin production</i>	PROC8b	Transfer of substance or mixture (charging and discharging) at dedicated facilities
<i>Epoxy Resin production</i>	PROC5	Mixing or blending in batch processes
<i>Epoxy Resin application</i>	PROC1	Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions
<i>Epoxy Resin application</i>	PROC2	Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions
<i>Epoxy Resin application</i>	PROC3	Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions
<i>Epoxy Resin application</i>	PROC4	Chemical production where opportunity for exposure arises
<i>Epoxy Resin application</i>	PROC5	Mixing or blending in batch processes
<i>Epoxy Resin application</i> <i>Epoxy Resin application</i>	PROC7 PROC8a	Industrial spraying Transfer of substance or mixture (charging and discharging) at non-dedicated facilities
<i>Epoxy Resin application</i>	PROC8b	Transfer of substance or mixture (charging and discharging) at dedicated facilities
<i>Epoxy Resin application</i>	PROC9	Transfer of substance or mixture into small containers (dedicated filling line, including weighing)
<i>Epoxy Resin application</i> <i>Epoxy Resin application</i>	PROC10 PROC13	Roller application or brushing Treatment of articles by dipping and pouring

Table 105: ECETOC TRA Operational Conditions and Risk Management Measures

Manufacturing	
Use	Industrial
Is substance a solid?	Yes
Dustiness (if it is solid)	low
Duration of activity	> 4 hours
Use of ventilation	Indoors with good general ventilation
Use of respiratory protection	no
Substance in preparation	> 25%
Dermal PPE	Gloves APF 5
Polycarbonate production	
Use	Industrial
Is substance a solid?	Yes
Dustiness (if it is solid)	low
Duration of activity	> 4 hours
Use of ventilation	Indoors with good general ventilation
Use of respiratory protection	no
Substance in preparation	> 25%
Dermal PPE	Gloves APF 5
Epoxy resin production	
Use	Industrial
Is substance a solid?	Yes
Dustiness (if it is solid)	low
Duration of activity	> 4 hours
Use of ventilation	Indoors with good general ventilation
Use of respiratory protection	no
Substance in preparation	> 25%
Dermal PPE	Gloves APF 5
PC bottle production	
Use	Industrial
Is substance a solid?	Yes
Dustiness (if it is solid)	low
Duration of activity	> 4 hours
Use of ventilation	Indoors with good general ventilation
Use of respiratory protection	no
Substance in preparation	< 1 %
Dermal PPE	Gloves APF 5
Epoxy paint production	
Use	Industrial
Is substance a solid?	No
Dustiness (if it is solid)	-
Duration of activity	> 4 hours
Use of ventilation	Indoors with good general ventilation
Use of respiratory protection	no
Substance in preparation	<1%
Dermal PPE	Gloves APF 5

Table 106: Results of the environmental exposure assessment in Step 2 (early innovation) – polycarbonate application

	BPA					BPAP					Isosorbide				
	Surface water	Sea water	Surface water sediment	Sea water sediment	Natural soil	Surface water	Sea water	Surface water sediment	Sea water sediment	Natural soil	Surface water	Sea water	Surface water sediment	Sea water sediment	Natural soil
ERC 1	663.55	27.70	10.12	0.00	25.24	846.88	35.36	12.90	0.00	24.89	3.94E-10	7.54E-17	4.53E-20	0.00	6.02E-13
RCR	28.85	12.04	0.02	0.00	0.05	76.99	32.14	0.01	0.00	0.01	5.23E-15	1.00E-20	7.62E-25	0.00	6.53E-17
ERC 6c	416.76	17.40	6.35	0.00	18.75	413.31	17.26	6.29	0.00	14.58	3.94E-10	7.40E-17	3.69E-20	0.00	1.48E-14
RCR	18.12	7.57	0.01	0.00	0.04	37.57	15.69	2.97E-03	0.00	0.01	5.23E-15	9.87E-21	6.20E-25	0.00	1.61E-18
ERC 5	104.80	4.38	1.60	0.00	5.40	132.38	5.53	2.02	0.00	5.56	9.86E-11	3.64E-17	1.81E-20	0.00	4.85E-12
RCR	4.56	1.90	2.49E-03	0.00	0.01	12.03	5.02	9.50E-04	0.00	3.23E-03	1.31E-15	4.85E-21	3.05E-25	0.00	5.26E-16

Table 107: Results of the environmental exposure assessment in Step 2 (early innovation) – epoxy resin application

	BPA					BPAP					Isosorbide				
	Surface water	Sea water	Surface water sediment	Sea water sediment	Natural soil	Surface water	Sea water	Surface water sediment	Sea water sediment	Natural soil	Surface water	Sea water	Surface water sediment	Sea water sediment	Natural soil
ERC 1	663.55	27.70	10.12	0.00	25.24	846.88	35.36	12.90	0.00	24.89	3.94E-10	7.54E-17	4.53E-20	0.00	6.02E-13
RCR	28.85	12.04	0.02	0.00	0.05	76.99	32.14	0.01	0.00	0.01	5.23E-15	1.00E-20	7.62E-25	0.00	6.53E-17
ERC 6a	39.34	1.64	0.60	0.00	4.78	48.88	2.04	0.74	0.00	4.91	3.94E-11	5.46E-17	1.09E-20	0.00	4.85E-12
RCR	1.71	0.71	9.37E-04	0.00	0.01	4.44	1.86	3.51E-04	0.00	2.86E-03	5.23E-16	7.28E-21	1.83E-25	0.00	5.26E-16
ERC 5	167.11	6.98	2.55	0.00	8.61	211.03	8.81	3.21	0.00	8.86	3.94E-10	8.10E-17	4.04E-20	0.00	7.11E-12
RCR	7.27	3.03	3.98E-03	0.00	0.02	19.18	8.01	1.51E-03	0.00	5.16E-03	5.23E-15	1.08E-20	6.79E-25	0.00	7.71E-16

Table 108: Results of the environmental exposure assessment in Step 2 (late innovation) – polycarbonate application

	BPA					BPAP					Isosorbide				
	Surface water	Sea water	Surface water sediment	Sea water sediment	Natural soil	Surface water	Sea water	Surface water sediment	Sea water sediment	Natural soil	Surface water	Sea water	Surface water sediment	Sea water sediment	Natural soil
ERC 1	663.55	27.70	10.12	0.00	25.24	846.88	35.36	12.90	0.00	24.89	3.94E-10	7.54E-17	4.53E-20	0.00	6.02E-13
RCR	28.85	1.46	0.01	0.00	0.01	76.99	32.14	0.01	0.00	0.01	3.69E-12	6.85E-18	1.13E-22	0.00	3.77E-14
ERC 6c	416.76	17.40	6.35	0.00	18.75	413.31	17.26	6.29	0.00	14.58	3.94E-10	7.40E-17	3.69E-20	0.00	1.48E-14
RCR	18.12	0.92	0.01	0.00	0.01	37.57	15.69	2.97E-03	0.00	0.01	3.69E-12	6.73E-18	9.23E-23	0.00	9.25E-16
ERC 5	104.80	4.38	1.60	0.00	5.40	132.38	5.53	2.02	0.00	5.56	9.86E-11	3.64E-17	1.81E-20	0.00	4.85E-12
RCR	4.56	0.23	1.33E-03	0.00	1.46E-03	12.03	5.02	9.50E-04	0.00	3.23E-03	9.22E-13	3.31E-18	4.54E-23	0.00	3.03E-13

Table 109: Results of the environmental exposure assessment in Step 2 (late innovation) – epoxy resin application

	BPA					BPAP					Isosorbide				
	Surface water	Sea water	Surface water sediment	Sea water sediment	Natural soil	Surface water	Sea water	Surface water sediment	Sea water sediment	Natural soil	Surface water	Sea water	Surface water sediment	Sea water sediment	Natural soil
ERC 1	663.55	27.70	10.12	0.00	25.24	846.88	35.36	12.90	0.00	24.89	3.94E-10	7.54E-17	4.53E-20	0.00E+00	6.02E-13
RCR	28.85	1.46	0.01	0.00	0.01	76.99	32.14	0.01	0.00	0.01	3.69E-12	6.85E-18	1.13E-22	0.00E+00	3.77E-14
ERC 6a	39.34	1.64	0.60	0.00	4.78	48.88	2.04	0.74	0.00	4.91	3.94E-11	5.46E-17	1.09E-20	0.00	4.85E-12
RCR	1.71	0.09	5.00E-04	0.00	1.29E-03	4.44	1.86	3.51E-04	0.00	2.86E-03	3.69E-13	4.96E-18	2.72E-23	0.00	3.03E-13
ERC 5	167.11	6.98	2.55	0.00	8.61	211.03	8.81	3.21	0.00	8.86	3.94E-10	8.10E-17	4.04E-20	0.00	7.11E-12
RCR	7.27	0.37	2.12E-03	0.00	2.33E-03	19.18	8.01	1.51E-03	0.00	0.01	3.69E-12	7.36E-18	1.01E-22	0.00	4.44E-13

Abstract Eurotox 2024

A computational toolbox supporting the development of Safe and Sustainable by Design chemicals and materials

D. A. Sarigiannis^{a, b, c, d}, F. Nikiforou^{a, b}, A. Karakoltzidis^{a, b}, A. Agallidou^{a, b}, Tomas Rydberg, Maja Halling, Chiara Laura Battistelli, Emilio Benfenati, Cecilia Bossa, Evert Bouman, Émilien Bourgé, Milena Brouwer-Milovanovic, Annabel Hill, Eleni Iacovidou, Ivo Iavicoli, Tomi Kanerva, Therese Kärnman, Veruscka Leso, Jenny Lindén, Magnus Lofstedt, Bernd Nowack, Araceli Sánchez Jiménez, Susanne Resch, Gianluca Selvestrel, Kirsi Siivola, Anezka Sharma, Vrishali Subramanian, Rosella Telaretti Leggieri, Martijn van Bodegraven, Joanke Van Dijk, Jaco Westra, Ziye Zheng, A. Gypakis, S. Karakitsios^{a, b}

^a HERACLES Research Center on the Exposome and Health, Center for Interdisciplinary Research and Innovation, Aristotle University of Thessaloniki, Thessaloniki, Greece

^b Environmental Engineering Laboratory, Department of Chemical Engineering, Aristotle University of Thessaloniki, Thessaloniki, Greece

^c University School of Advanced Study IUSS, Pavia, Italy

^d National Hellenic Research Foundation, Athens, Greece

The Safe and Sustainable by Design (SSbD) concept has been introduced to integrate the safety and sustainability aspects of chemicals and materials in a holistic way as early as possible, considering their entire life cycle. The SSbD framework addressed by the EC describes a five-step approach to the assessment of the safety and sustainability of a chemical or material, which is linked to the innovation process through the stage gate model. The five-step approach of the framework is organized so that the initial three steps relate to hazard and risk assessment, while the last two steps relate to environmental and socioeconomic sustainability assessment, respectively. The current paper presents the development and testing process of the alpha version of the SSbD toolbox under the auspices of the EU partnership on chemical risk assessment (PARC) project. The PARC toolbox aims to provide an innovative toolbox that facilitates the operationalization of the EC SSbD framework. The testing process of the alpha version of the toolbox was conducted by implementing a detailed case study, both in the early and late innovation stages. The aim of this case study was to evaluate the efficiency and complete potential of the toolbox, as well as to identify any inconsistencies in the results obtained from the different tools, in both innovation stages. The case study included the assessment of Bisphenol-A (BPA) in two different applications: the replacement of BPA in polycarbonate bottles and epoxy resin paints, using Bisphenol-AP (BPAP) and Isosorbide as alternatives. The only information considered during the early stages was the structure and the potential application of the chemical. A wide range of tools used including Quantitative structure-activity relationship (QSAR) models (VEGA, OECD QSAR toolbox, Janus, Oncologic, Mistra SafeChem in silico Toolbox, and Danish (Q)SAR database) for Step 1, models such as ECETOC TRA, ProScale, ART, Stoffenmanager, INTEGRA, ConsExpo, SimpleBox, CEM, and Vermeer FCM for Steps 2 and 3 and GaBi LCA for a preliminary/prospective Life Cycle Assessment (LCA) in Step 4. Based on the results, significant differences were observed in the outcomes when applying the models of Steps 2 and 3 in both innovation stages. These variations may arise due to the type and quality of input data (e.g. QSARs) used in both cases. Therefore, the evaluation of the reliability of predictions resulting from QSARs, as well as an uncertainty analysis of the results is of great importance. Moreover, the integration of New Approach Methodologies (NAMs) for hazard predictions during the middle innovation stages is highlighted. Additionally, the data scarcity during early innovation contributes to uncertainty in LCA results. In summary, this work has established a basis for the further development of the SSbD toolbox, aiming at improving its effectiveness and applicability.

Abstract 2024 AIChE Annual Meeting

A computational toolbox supporting the development of Safe and Sustainable by Design chemicals and materials

D. A. Sarigiannis^{a, b, c, d}, F. Nikiforou^{a, b}, A. Karakoltzidis^{a, b}, A. Agaliadou^{a, b}, Tomas Rydberg, Maja Halling, Chiara Battistelli, Emilio Benfenati, Cecilia Bossa, Evert Bouman, Émilien Bourgé, Milena Brouwer-Milovanovic, Annabel Hill, Eleni Iacovidou, Ivo Iavicoli, Tomi Kanerva, Therese Kärnman, Veruscka Leso, Jenny Lindén, Magnus Lofstedt, Bernd Nowack, Araceli Sánchez Jiménez, Susanne Resch, Gianluca Selvestrel, Kirsi Siivola, Anežka Sharma, Vrishali Subramanian, Rosella Telaretti Leggieri, Martijn van Bodegraven, Joanke Van Dijk, Jaco Westra, Ziye Zheng, A. Gypakis, S. Karakitsios^{a, b}

^a *HERACLES Research Center on the Exposome and Health, Center for Interdisciplinary Research and Innovation, Aristotle University of Thessaloniki, Thessaloniki, Greece*

^b *Environmental Engineering Laboratory, Department of Chemical Engineering, Aristotle University of Thessaloniki, Thessaloniki, Greece*

^c *University School of Advanced Study IUSS, Pavia, Italy*

^d *National Hellenic Research Foundation, Athens, Greece*

The European Union (EU), through the Chemicals Strategy for Sustainability (CSS) and the Zero Pollution Action Plan, has emphasized the imperative for an environment and economy that are both climate-neutral and toxic-free. This emphasis underscores a transition towards a Safe and Sustainable by Design (SSbD) approach, by integrating safety and sustainability considerations into the early design stages of chemicals and materials, focusing on the whole life cycle. SSbD aims to foster the chemical innovation process by developing and assessing novel and existing chemicals. This is achieved by adhering to circular economy principles, all while mitigating the potential negative impacts on human health, the environment and society in the short and long term. The EC introduced a framework for SSbD, which is a comprehensive five-step approach for the safety and sustainability assessment of chemical and materials. The first three steps involve safety assessment including hazard, occupational exposure, environmental exposure, and consumer exposure. The last two steps are related to the sustainability assessment including environmental and socioeconomic aspects.

Within the EU partnership on chemical risk assessment (PARC), the PARC SSbD toolbox is being developed. The PARC toolbox aims at the operationalization of the EC framework, by providing an integrative and innovation toolbox for both innovators and regulators. It will include all the relevant data, methods and tools for SSbD, along with automated pipelines that encompass every step of the framework across the stages of innovation. The tools will be structured and mapped in accordance with the stages of chemical or material development into a phased commercial product development (stage-gate model) and the five steps of the EC framework. The PARC toolbox is based upon a methodological framework (in development) that leverages advanced methods for hazard, exposure, human health risk assessment, and sustainability assessment. Initiating from user-provided data including chemical structure parameters and a designated parameter list, a range of tools with varying levels of complexity will be employed to facilitate the SSbD assessment across innovation process.

The development of the alpha version of the toolbox is currently underway. As part of this development process, a detailed case study was conducted to explore the toolbox's full potential and to discern any disparities in the findings between the two stages as well as between the different tools used. The case study included the assessment of Bisphenol-A (BPA) and two potential alternative substances; Bisphenol-AP and Isosorbide. The selected substances underwent evaluation in two distinct applications: as a BPA

alternative for polycarbonate bottles and as a BPA replacement in epoxy resin paints. To determine the efficiency of the toolbox, the case study was conducted in both the early and late stages of innovation. In the early innovation, only the structure and the potential application of the substance were considered as input information. In the context of late innovation, the assessment process was informed by data derived from pertinent databases (e.g. ECHA Database, EFSA, PubChem, CompTox Chemical Dashboard) or from relevant studies. In both scenarios, a range of tools was used to perform the SSbD assessment.

In early innovation, Quantitative structure-activity relationship (QSAR) models, such as VEGA, OECD QSAR toolbox, Janus, Oncologic, Mistra SafeChem *in silico* Toolbox and Danish (Q)SAR database, were applied in Step 1 to predict the hazard endpoints (e.g. carcinogenicity, mutagenicity, reproductive toxicity, endocrine disruption) requested in the EC JRC framework. In Steps 2 (manufacturing and processing phase) and 3 (use phase), a number of models, including ECETOC TRA, ProScale, ART, Stoffenmanager, INTEGRA, ConsExpo, SimpleBox, CEM and Vermeer FCM, were employed to forecast potential risks relating to occupational, environmental, and consumer exposure. These models were used in both early and late innovation, and it was found that there were differences in their outcomes. The observed difference in the results between the early and late stages of innovation can be attributed to the source of input data used. Specifically, the former relied on QSAR predictions while the latter was based on experimental measurements. In Step 4, a preliminary Life Cycle Assessment (LCA) was conducted to evaluate the environmental sustainability in early innovation.

Assessment was performed using the GaBi LCA software, which is a widely recognized tool for conducting LCAs. Lastly, the exploration of Step 5, the socioeconomic analysis step, was very limited. Overall, QSAR models, played a vital role in predicting hazards and physicochemical properties during early innovation when data availability was limited. In addition, variations in SSbD scores for Steps 1-3 were observed, with the selection of QSARs and the available data level influencing the results. Therefore, it is of great importance to evaluate the reliability of predictions resulting from QSARs and to perform an uncertainty analysis of the results from different tools. As a result, integrating New Approach Methodologies (NAMs) with QSARs to assess hazard potency is highly significant. Moreover, a need for further development of models for endocrine disruption and immunotoxicity prediction is highlighted. Finally, it is crucial to develop, test, and incorporate reliable predictive models for toxicity and tools for prospective LCA and socioeconomic assessment. In particular for LCA in early innovation, the lack of data regarding up- and downstream life cycle stages contributes to results uncertainty and better guidance on how to populate the model is required.

In conclusion, the concept of SSbD is characterized by a high level of complexity arising from the diverse types of assessments essential for its implementation. This study has established a basis for the further refinement of the SSbD toolbox, aiming to enhance its efficacy and applicability and will eventually foster cohesion across diverse policies and strategies. The SSbD toolbox will be a guidance tool that will include all the relevant data, tools and methods for the operationalization of SSbD, while focusing on the integration of risk and sustainability assessment.

Abstract SETAC Europe 2024

Testing tools for suitability for SSbD in early phases of innovation, applied to BPA and alternatives

Tomas Rydberg¹, Maja Halling¹, Ivo Iavicoli², Spyros Karakitsios³, Veruscka Leso², Magnus Løfstedt⁴, Fotini Nikiforou³, Bernd Nowack⁵, Denis Sarigiannis³, Vrishali Subramanian⁶, Rosella Telaretti Leggieri¹, Joanke Van Dijk⁵, Jaco Westra⁶

¹IVL Swedish Environmental Research Institute, Sweden, ²University of Naples Federico II, Italy, ³Aristotle

University of Thessaloniki, Greece, ⁴European Environment Agency, Denmark, ⁵Empa-Swiss Federal Laboratories for Materials Science and Technology, Switzerland, ⁶National Institute for Public Health and the Environment (RIVM), The Netherlands

E-mail contact: tomas.rydberg@ivl.se

1. Introduction

Within the PARC project (<https://www.eu-parc.eu/>), gathering a large number of research organisations and public bodies, one Task deals with Safe and Sustainable by Design for chemicals and materials, SSbD, in relation to the framework described by the European Commission in a recent study [1]. Experience of applying the suggested SSbD framework is so far limited. Various EU projects (e.g. PARC, IRISS) and national initiatives (e.g. Mistra SafeChem in Sweden) are in the process of advancing and/or evaluating tools for SSbD for a range of use cases. The authors are co-leading the work within PARC to test tools in case studies for SSbD and reports here on advancements in a case study on Bisphenol-A and selected alternatives.

2. Materials and Methods

2.1. Selection of tools

The choice of tools was primarily based on those that had already been evaluated within the program, but also new tools from other partners were included. The aim was to include at least one tool applicable to each stage of the JRC framework. Each JRC step has been included in the study, with an emphasis on tools applicable in step 1, mainly QSAR – based tools.

2.2. Workflow

Each participant was asked to apply the tool to bisphenol A (BPA) and two BPA alternatives, Isosorbide and BPAP. In choosing the BPA alternative, we wanted to test a bisphenol and a substance that would be bio-based. The aim of the tool test was not to find an optimal alternative to BPA, but rather to test the tools and the toolbox.

The premises in the case study was that only the structure and the intended application of the three substances was given as input data when running the tools. The following two applications was chosen for the study:

- Epoxy resins in paint
- Polycarbonate reusable water bottles

All tool testing participants were asked if their tool could be run with the given information, structure and application. If “yes” the participant ran the tool and the results were compiled and analyzed.

If the tool needed more input than structure and application, the tool tester was asked to document what input that would be needed to run the tool and what other tools that may contribute with needed input data. Each tool testing participant was asked to describe what tools and what assumptions that would be needed in order to be able to run the tool. Tools applicable in step 1 would for obvious reasons have a shorter road to operation compared to tool applicable to step 4 and 5. If the tool tester knew how to generate the input data needed to run their tool, they were asked to use these tools to generate the data needed. Documentation from each tool tester was compiled in a report and results from test runs were analyzed. Results from tool in step 1 were compared among themselves and against reference data to evaluate the consistency and precision of the prediction.

3. Results and Discussion

By providing limited information on the substance, we wanted to create a situation that mimics that of the early development stage of a chemical. How much can you predict from very limited knowledge about a substance?

The aim was also to force tool owners and tool testers to use the tools even though the indata were only based on assumptions and output from tools from previous steps in the framework. We wanted to show that if all tools can be used when indata is based on educated assumptions, expert evaluation and collected experience.

4. Conclusions

Initial findings:

- The complexity of SSbD lies in the breadth of assessment types that is required to cover the whole framework
- Safety and sustainability aspects have traditionally been dealt with separately; experts in the two domains have different backgrounds, training, and use of words. A lot of effort is needed to create a common understanding of SSbD.
- In early phases of innovation qualitative expert judgement, semi-quantitative models, and computational models, all have a role to play. Interestingly, this is a common denominator for all SSbD steps. And predictive models are needed, and are also available, for all steps.

5. References

[1] Caldeira C, et al. 2022. Safe and sustainable by design chemicals and materials - Framework for the definition of criteria and evaluation procedure for chemicals and materials, EUR 31100 EN, Publications Office of the European Union, Luxembourg, 2022, ISBN 978-92-76-53264-4, doi:10.2760/487955, JRC128591.

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Safe and sustainable by Design chemicals and materials (SSbD): First broad testing of tools for early stages of innovation and substitution

Tomas Rydberg, Anna Agaliadou, Chiara Battistelli, Emilio Benfenati, Cecilia Bossa, Evert Bouman, Émilien Bourgé, Swapnil Chavan, Maja Halling, Annabel Hill, Eleni Iacovidou, Ivo Iavicoli, Tomi Kanerva, Spyros Karakitsios, Achilleas Karakoltzidis, Veruscka Leso, Magnus Lofstedt, Foteini Nikiforou, Ulf Norinder, Bernd Nowack, Araceli Sánchez Jiménez, Denis Sarigiannis, Gianluca Selvestrel, Kirsi Siivola, Vrishali Subramanian, Rosella Telaretti Leggieri, Martijn van Bodegraven, Joanke Van Dijk, Jaco Westra, Ziye Zheng

ABSTRACT

Safe and Sustainable by Design (SSbD) has the potential to be a powerful concept and methodological framework for innovation in the chemical sector. The Partnership for the Assessment of Risks from Chemicals (PARC) [1] aims a.o. to build an SSbD toolbox to steer the chemical industry towards innovation that is aligned with the European Green Deal and Chemicals Strategy for Sustainability. In this PARC study, existing tools relevant for the application of the SSbD framework outlined by JRC [2] were tested in a pilot case study on bisphenol A (BPA) and two alternatives, bisphenol AP (BPAP) and isosorbide (ISB), in the two applications polycarbonate food-contact bottles and epoxy resins.

The purpose was to test the tools' function in the context of the JRC framework, not to select an alternative to BPA in the chosen applications. Furthermore, we combined the JRC framework with an innovation model in several stages. We aimed to focus on early stages with limited data availability, thus provided tool testers with only the chemicals' name and structure and the intended application, and then asked them to specify what additional information is needed for running the tool.

Existing tools were identified by a thorough review and were tentatively mapped according to the stage gate innovation model and the "steps" (or components) of the SSbD framework. For Step 1 ("Hazard") we tested: VEGA, JANUS, Oncologic, MSC in silico toolbox, INTEGRA, Danish (Q)SAR database and QSAR Toolbox. For Step 2 ("Process safety"): ProScale, INTEGRA, ECETOC TRA, Advanced Reach Tool ART and Stoffenmanager. For Step 3 ("Use phase"): VEGA, INTEGRA, ECETOC TRA, ConsExpo and SimpleBox. For Step 4 ("Environmental sustainability"): GaBi and quasaLCA). For Step 5 ("Social and economic sustainability"), we tested the Social LCA framework of UNEP, as well as an approach developed within the H2020 SUNSHINE project.

Some initial observations include:

Different tools are needed to cover the indicators requested in the JRC SSbD framework, also within each step. Tools intended for the same purpose partly align and partly differ in output, also when assessing the same end-point (indicator). This seems to lead to the need for very specific guidance when defining qualification criteria for SSbD, e.g. prescribing a specific set of tools and a decision approach to reach conclusions from multiple tools.

The further advancement of SSbD in innovation will have to see a development of qualitative expert judgement, semi-quantitative models, and computational models, for all SSbD steps.

References

[1] <https://www.eu-parc.eu>

[2] Caldeira, C., Farcas, R., Garmendia Aguirre, I., Mancini, L., Tosches, D., Amelio, A., Rasmussen, K., Rauscher, H., Riego Sintes, J. and Sala, S., Safe and sustainable by design chemicals and materials - Framework for the definition of criteria and evaluation procedure for chemicals and materials, EUR 31100 EN, Publications Office of the European Union, Luxembourg, 2022, ISBN 978-92-76-53280-4, doi:10.2760/404991, JRC128591

Key words

Innovation, Safety, Sustainability, Design, Chemicals

List of SSbD related research projects

Project	Title	TOPIC
TOXBOX	Toxicology-testing platform integrating immunocompetent in vitro/ex vivo modules with real-time sensing and machine learning based in silico models for life cycle assessment and SSbD	HORIZON-CL4-2023-RESILIENCE-01-21
CheMatSustain	IMPLEMENTING INNOVATIVE METHODS FOR SAFETY AND SUSTAINABILITY ASSESSMENTS OF CHEMICALS AND MATERIALS PARTICULARLY AT NANO LEVEL IN THE EUROPEAN UNION	HORIZON-CL4-2023-RESILIENCE-01-21
CHIASMA	Accessible Innovative Methods for the Safety & Sustainability Assessment of Chemicals & Materials	HORIZON-CL4-2023-RESILIENCE-01-21
SSbD4Chem	Safe and Sustainable by Design framework for the next generation of Chemicals and Materials	HORIZON-CL4-2023-RESILIENCE-01-21
ANALYST	STRENGTHENING THE INTEGRATED APPROACH OF HOLISTIC IMPACT ASSESSMENTS FOR SAFE AND SUSTAINABLE BY DESIGN PLASTIC VALUE CHAIN	HORIZON-CL4-2023-RESILIENCE-01-22
INTEGRANO	Multidimensional Integrated Quantitative Approach to Assess Safety and Sustainability Of Nanomaterials In Real Case Life Cycle Scenarios Using Nanospecific Impact Categories	HORIZON-CL4-2023-RESILIENCE-01-22
INSIGHT	Integrated Models for the Development and Assessment of High Impact Chemicals and Materials	HORIZON-CL4-2023-RESILIENCE-01-22
SUNRISE	Safe and sUstainable by designN: integRated approaches for Impact aSsessment of advanced matERials	HORIZON-CL4-2023-RESILIENCE-01-22
AI-TranspWood	AI-driven multiscale methodology to develop Transparent Wood as sustainable functional material	HORIZON-CL4-2023-RESILIENCE-01-23
PINK	Provision of Integrated Computational Approaches for Addressing New Markets Goals for the Introduction of Safe-and-Sustainable-by-Design Chemicals and Materials	HORIZON-CL4-2023-RESILIENCE-01-23
SiToLub	Simulation Tools for the design of safe and sustainable Lubricants	HORIZON-CL4-2023-RESILIENCE-01-23
M2DESCO	Computational Multi-Models Enabled Design of Safe &	HORIZON-CL4-2023-RESILIENCE-01-23

	Sustainable Multi-Component High-Entropy Coatings	
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