GreenSolRes

Deliverable 4.1

Gap analysis for the data required for safety assessment and strategy for data completion

Demonstration of solvent and resin production from lignocellulosic biomass via the platform chemical levulinic acid

The project leading to this application has received funding from the Bio Based Industries Joint Undertaking under the European Union's Horizon 2020 research and innovation programme under grant agreement No 720695

BBI JU

Bio-based Industries Consortium

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About GreenSolRes

The need to establish economic and sustainable large-scale operations for the conversion of renewable resources to chemical building blocks is becoming increasingly urgent in the context of climate change and depleting fossil fuel reservoirs. Pathways for manufacturing of bio-based fuels and chemicals have been developed but most of them rely on sugar and starch crops for feedstock. GreenSolRes aims at a sustainable and competitive industrial production of the platform chemical levulinic acid (LVA) from lignocellulosic wastes and residues originating from forestry and agricultural sector. Further, the conversion of LVA into industry relevant building blocks γ-valerolactone (GVL), 1-methyl-1,4-butanediol (MeBDO) and 2-methyltetrahydrofuran (2-MTHF) will take place by new catalytic methods developed during the course of this project. Finally, these chemicals will be upgraded to solvents and resin monomers for the production of high added value adhesives and consumer products. This project was started in September 2016 and has a duration of five years.

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About this document

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Publishable Summary

This report reflects the results of the literature review on the physical-chemical properties, human toxicity and ecotoxicity data (hazard assessment), and environmental fate (biodegradation, bioaccumulation) of levulinic acid, the biomass derived chemicals from the levulinic acid pathway (2-methyltetrathydrofuran, gamma-valerolactone and 1,4-pentanediol) and their respective fossil-based benchmarks (gamma-butyrolactone, 1,4-butanediol and tetrahydrofuran).
A summary of the results of the literature review on physical-chemical properties, human toxicity, ecotoxicity and environmental fate are presented in the tables below. Based on these results, data gaps were identified and a strategy for data completion is proposed.

Literature review: physical-chemical properties

The physical-chemical properties that are high impact determinants in the risk assessment of chemical substances are the water solubility, the vapour pressure and the octanol-water partition coefficient (Kow). The latter is low for all substances. If no measured data were available, the property value was estimated with computer models. There is no data gap for these three physical-chemical properties.

Substance	Water solubility	Vapour pressure 20°C	Log Kow	Source (unless indicated otherwise)
Levulinic acid	791.3 g/l	0.374 Pa (25°C)	-0.497	REACH dossier
Tetrahydrofuran	100 g/l	17 kPa	0.45	REACH dossier
2-Methyltetra-hydrofuran	143 mg/l at 20°C (Glass *et al*., 2017)	14 kPa (25°C) (estimated)	1.1	REACH dossier
γ-butyrolactone	>1000 g/l	34.4 Pa	-0.566	REACH dossier
γ-valerolactone	≥100 g/l	51.1 Pa at 25°C	0.11 (estim.)	PubChem, EUSES model
1,4-butanediol	636 g/l (estim. by Episuite)	0.725 Pa (estim. by Episuite)	-0.88	REACH dossier
1,4-pentanediol	76.64 g/l (estim.)	6.05 Pa (estim.)	0.20 (estim.)	Episuite

Literature review: human health

Based on CLP[1] criteria for each of the endpoints, certain compounds could be classified as toxic (red box) or not toxic (green box). In case of insufficient information or uncertain information (sometimes conflicting data) to classify for toxicity, orange/yellow shaded area is given. No colour is given in case there were no data found in any of consulted sources. The summary information in the following table is the starting point for the proposed test strategy to complete data gaps.

[1] Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures

Summary table health effects for main toxicological endpoints (part 1)

Endpoint	LVA	THF	2-MTHF	GBL	GVL	BDO	PDO
Acute tox. Oral exposure					no data		no data
Acute tox. Inhalation	no data				no data		no data
Acute tox. Dermal exposure				no data	no data		no data
Irritation Skin					no data		no data
Irritation Eye					no data		no data
Sensitisation Skin					no data		no data
Sensitisation Respiratory	no data	no data	no data	no data	no data	no data	no data

Summary table health effects for main toxicological endpoints (part 2)

Endpoint	LVA	THF	2-MTHF	GBL	GVL	BDO	PDO
Repeated dose toxicity – oral	Testing proposal[2]	NOAEL ~ 113 mg/kg bw	NOAEL= 250 mg/kg bw	NOAEL= 225 -400 mg/kg bw	no data	NOAEL= 50-200 mg/kg bw	no data
Repeated dose toxicity – other route	no data	NOAEC = 0,6 mg/l (inhalation)	Testing proposal	no data	no data	NOAEC = 5,2 mg/l (inhalation)	no data
Genotoxicity	negative	negative	negative	negative	no data	negative	no data
Carcinogenicity	no data		QSAR		no data	Read across	no data
Reproduction toxicity	Testing waived based on exposure	*LOEC: 8000-9000 ppm (dw)	no data	Read across	no data	NOAEL ≥800 mg/kg bw/ day	no data
Development toxicity	Testing proposal	*LOEC=5000 ppm (vapour)	Testing proposal	NOAEL ≥500 mg/kg bw/ day	no data	NOAEL = 100 mg/kg bw/day	no data

**threshold value for toxicity, but not specific for reproduction/developmental toxicity*

Literature review: environmental effects

Based on CLP criteria for acute and chronic toxicity, certain compounds could be classified as (very) toxic (red box), harmful (orange box) or not toxic (green box). In case of lack of data, the box colour is grey. The latter information is the starting point for the proposed test strategy to complete data gaps.

The classification is based on the most sensitive species (fish, invertebrates (Daphnia) or algae).

[2] In REACH registration dossier

Endpoint	LA	THF	MTHF	GBL	GVL	BDO	PDO
Acute					estimated		estimated
Chronic				no data	no data		no data
STP*					no data		no data

* Sewage treatment plant (acute)

Substances are classified as readily biodegradable (green box), inherently biodegradable (orange box) or not readily biodegradable (red box) in the table below. If no information is available from biodegradation studies, the biodegradation was estimated with a computer model. The information in the table is the starting point for the proposed test strategy to complete data gaps.
All substances are expected to have a low bioaccumulation potential. There is no data gap for bioaccumulation.

Endpoint	LA	THF	MTHF	GBL	GVL	BDO	PDO
Biodegradation			no data		estimated		estimated
Bioaccumulation					estimated		

Proposal of test strategy for data completion

Based on these results of data review for human health and environmental effects, data gaps were identified and the following testing strategy is proposed.

In the table below an overview is given of human toxicological endpoints and type of samples which will be considered in the 1st step of testing. Some optional testing is foreseen but can be decided after 1st phase considering time and budget limits.

Proposal of test plan for toxicity tests related to human health endpoints

Sample	Skin irritation/ corrosion* RHE/Corrositex	Eye irritation* BCOP/HCE	Genotoxicity Ames	Developmental toxicity Zebrafish embryo
LVA biobased/ commercial	optional	optional	optional	optional
Benchmark THF	/	/	/	optional
2-MTHF biobased/ commercial	X	X	X	optional
Benchmark GBL	X	X	X	optional
GVL biobased/ commercial	X	X	X	optional
Benchmark BDO	X	X	X	optional
PDO biobased/ commercial	X	X	X	optional

*strategy of testing to allow categorisation

The test plan to assess acute and chronic ecotoxicity for the aquatic environment is presented in next table. Limit tests will be run (100 mg/l), prior to evaluation of test compounds in a dilution series. The results of the acute toxicity will serve as a range finding for the chronic toxicity tests. In the 1st step, biodegradation testing and terrestrial toxicity will not be covered. The latter endpoint might be evaluated in a 2nd stage if based on predicted emission there is a need to obtain toxicity data for the terrestrial compartment.

Proposal of test plan for ecotoxicity assessment (aquatic)

Sample	**Aquatic toxicity - acute** Algae/invertebrate/fish**	**Aquatic toxicity – chronic*** Invertebrate/fish**
LVA biobased/ commercial	optional	optional
Benchmark THF	/	/
2-MTHF biobased/ commercial	X	X
Benchmark GBL	X	X
GVL biobased/ commercial	X	X
Benchmark BDO	X	X
PDO biobased/ commercial	X	X

*only in case acute toxicity < 100 mg/l; ** zebrafish embryo/larvae

Abbreviations

atm	atmosphere
BDO	1,4-butanediol
bw	body weight
Clint	Intrinsic clearance
C&L	Classification and labelling
CLP	Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures
CNS	Central Nervous System
d	days
dw	dry weight
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EU	European Union
EUSES	European Union System for the Evaluation of Substances
g	gram
GBL	gamma-butyrolactone
GHB	gamma-hydroxybutyric acid (metabolite of GBL)
GVL	gamma-valerolactone
IARC	International Agency for Research on Cancer
kg	kilogram
l	liter
LVA	levulinic acid
2-MTHF	2-methyltetrahydrofuran
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
PDE	Permitted daily exposure
PDO	1,4-pentanediol
PBPK	physiologically-based, pharmacokinetic model
PNEC	Predicted No Effect Concentration
QSAR	Quantitative Structure Activity Relationship
REACH	Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)
SI	Stimulation index (e.g. LLNA test with ^{3}H-thymidine incorporation)
TG	Test Guideline
THF	tetrahydrofuran
WoS	Web of Science