SAFE AND SUSTAINABLE BY DESIGN WITHIN UNILEVER

Application of Safe and Sustainable by Design Approaches for a Biosurfactant

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Introduction

Unilever is a global fast-moving consumer goods company, marketing many of the world's largest and most well-known Home Care, Beauty & Wellbeing, Personal Care, Nutrition and Ice Cream brands. Ensuring products are safe for consumers, workers and the environment is of paramount importance and is enshrined within corporate policy, while the Unilever corporate *Compass Strategy*[1] commits the company to grow whilst improving the sustainability of its products and operations. Business Group innovation strategies reflect the corporate Compass, embedding the sustainability challenge in their future looking (advanced) material and technology plans.

Safe and sustainable design of products has long been an essential part of Unilever's innovation process. R&D teams engage our safety and sustainability scientists at the earliest stage of innovation to build safety and sustainability considerations, alongside consumer needs, into new ingredient and product design. Safety considerations focus on consumer, occupational and environmental safety, whilst environmental sustainability impacts are assessed across the product life cycle.

Given the company vision[2], the Compass strategy and the long-standing commitment to safe and sustainable product design practices, Unilever is a strong supporter of the objectives of the European Green Deal. A key element of the transition of EU society to a more sustainable future is the development of new chemicals that are safe and sustainable by design and the 2022 JRC report "*Safe and Sustainable Chemicals and materials: Framework for the definition and evaluation procedure for chemicals and materials*"[3] proposes a framework to support achieving this.

In this report, we reflect on the framework proposed by the JRC: in Part I, we provide an innovation case study - a biosurfactant for use within a Home Care product - to describe the approaches currently taken within Unilever to design-in safety and sustainability; and in Part II, we provide a downstream user point of view and recommendations for further development of the JRC SSbD framework.

Summary of Key Points and Recommendations

Our belief is that sustainable product innovation can only be truly embedded in company operations if an enabling environment is offered both by the external policy context (e.g., as per the objectives of the European Green Deal) and individual business strategies. Company vision, strategy and culture are essential: the SSbD framework may help to embed safe and sustainable design considerations at an operational level, but will only be effective if company culture is conducive.

For the SSbD framework to be most effective, we would recommend the following:

- Reconsider the conceptual framing, moving away from absolute safety and sustainability assessment: we believe this is not a viable / desirable ambition.

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[1] Unilever Compass Strategy: https://www.unilever.com/files/8f9a3825-2101-411f-9a31-7e6f176393a4/the-unilever-compass.pdf

[2] Our Vision is to deliver winning performance by being the global leader in sustainable business (Unilever Compass Strategy).

[3] Caldeira et al. 2022. https://publications.jrc.ec.europa.eu/repository/handle/JRC128591.

- Ensure alignment to the existing stage gate innovation process, with explicit acknowledgement of the need for iterative and parallel assessment of both safety and sustainability elements that accounts for data availability and methodological feasibility at each stage.
- An approach for dealing with trade-offs (within and between criteria) is needed that encourages adoption within industry and truly supports movement towards the transition of more safe and sustainable chemicals.
- Support sector-based initiatives to generate and share data, methodologies and approaches relevant for SSbD assessments (e.g. data for new and existing chemicals).
- Focus further developments of the SSbD framework on:
    - Tier 1 pre-assessment / early-stage screening (e.g. rule-bases, question-sets etc.) especially non-animal NAMs, helping to guide innovation in future-looking advanced chemicals and materials.
    - Mechanisms to accommodate new safety and sustainability assessment approaches into the SSbD framework as these develop.

Part I: Safe and Sustainable Design – Unilever approach

Innovation at Unilever

Innovating new products with new or improved consumer benefits and/or sustainability profiles is a core process within Unilever to drive brand growth. The process is structured around several investment 'decision gates' to enable innovation to progress and assess alignment with corporate and brand strategy. Safety and sustainability are critical elements of each innovation phase and the decision-making at each decision gate. Our safety and sustainability scientists are engaged early and ongoing in the innovation process by R&D scientists to ensure safety and sustainability are designed-in from first principles. This cross-functional collaboration continues throughout the innovation process with evaluation of technologies moving from early-stage screening through staged safety and sustainability assessments. Depending on the complexity or disruptive nature of the innovation, the scale of the supporting safety and sustainability programmes can vary. For instance, minimal work may be required when considering minor changes to existing products while major work is often needed to evaluate novel product technologies, especially when existing knowledge of their use in consumer products is lacking.

Innovation of Biosurfactants

Surfactants are a critical component of cleaning products, with traditional sources of surfactants involving the use of non-renewable fossil fuel derived carbon. To reduce reliance on fossil carbon and create more circular carbon systems, Unilever has committed to "*Replace fossil-fuel derived carbon with renewable or recycled carbon in all our cleaning and laundry product formulations by 2030*"[4]. Chemical ingredients contribute 46% of the life cycle carbon footprint of Unilever's cleaning and laundry products. By transitioning away from fossil fuel-derived chemicals in product formulations, alternative sources of carbon could also help reduce the carbon footprint of Home Care products.

Potential sources of carbon include captured CO_2 (e.g. from factory emissions), carbon from terrestrial plants, marine sources such as algae, and waste materials. Biosurfactants derived from biological sources of carbon (terrestrial and marine plants as well as some waste materials) may be produced through bacterial fermentation processes, in which renewable feedstocks such as sugar provide the food / energy source. These biosurfactants can either be chemically identical to traditional, fossil feedstock derived surfactants or have more novel structures and properties.

Here, we consider a novel biosurfactant intended for use in home care cleaning products – we take the example of a hand dishwash product. For this case study, we describe the early screening and staged assessment approaches used within Unilever to evaluate safety and sustainability throughout the innovation process. In this scenario, Unilever is a downstream user of a novel biosurfactant

[4] Unilever Compass Strategy: https://www.unilever.com/files/8f9a3825-2101-411f-9a31-7e6f176393a4/the-unilever-compass.pdf

sourced from a third-party manufacturer. Due to Unilever's global scale, any biosurfactant used within its core home care portfolio will be required at relatively high volume (e.g. >1,000 tpa).

Aspects considered in the Unilever safety and sustainability evaluation of the biosurfactant for the intended home care cleaning product include:

- Consumer safety at expected levels of inclusion in the product formulation, coupled with realistic worst-case estimates of consumer exposure under conditions of reasonable foreseeable use;
- Occupational safety associated with handling and formulating the ingredient into products within Unilever (or Unilever contracted) factories;
- Environmental safety of Unilever's total use of the ingredient, in all products containing the ingredient, and for each market in which it is sold;
- Environmental sustainability impacts across the life cycle of the ingredient and the products in which the ingredient would be used, compared to the current formulation or another appropriate benchmark product.

A 'safe and sustainable by design' mindset is well established within Unilever: determined with company vision and strategy, embedded in Business Group innovation strategies and plans and enabled by early-stage screening and staged assessment approaches aligned to key investment decision-gates. The biosurfactant case study presented in this section demonstrates the need for cross-functional teams (R&D teams plus safety and sustainability scientists, suppliers etc.) to collaborate closely during the full innovation process. Working in this way enabled superior functional benefits of the biosurfactant in formulation, whilst identifying and addressing all relevant safety hazards and risks (consumer, occupational and environmental) and assessing the most material environmental impacts, demonstrating impact reductions compared with existing formulations.

Figure 1 provides an overview of the innovation steps in Unilever, and the safety and sustainability approaches adopted at each stage for the evaluation of a biosurfactant intended for use within a home care cleaning product.

Table 1 provides a summary of the consumer, occupational and environmental safety and sustainability data that are available or generated at each innovation stage, along with the approaches applied for the evaluation of the biosurfactant for use within a home care cleaning product. This table is a summary of the detail provided in Annex 1.

Figure 1: Overview of typical safety and sustainability approaches used by Unilever described for four generic innovation stages and applied to the case study of a biosurfactant intended for use within a home care cleaning product

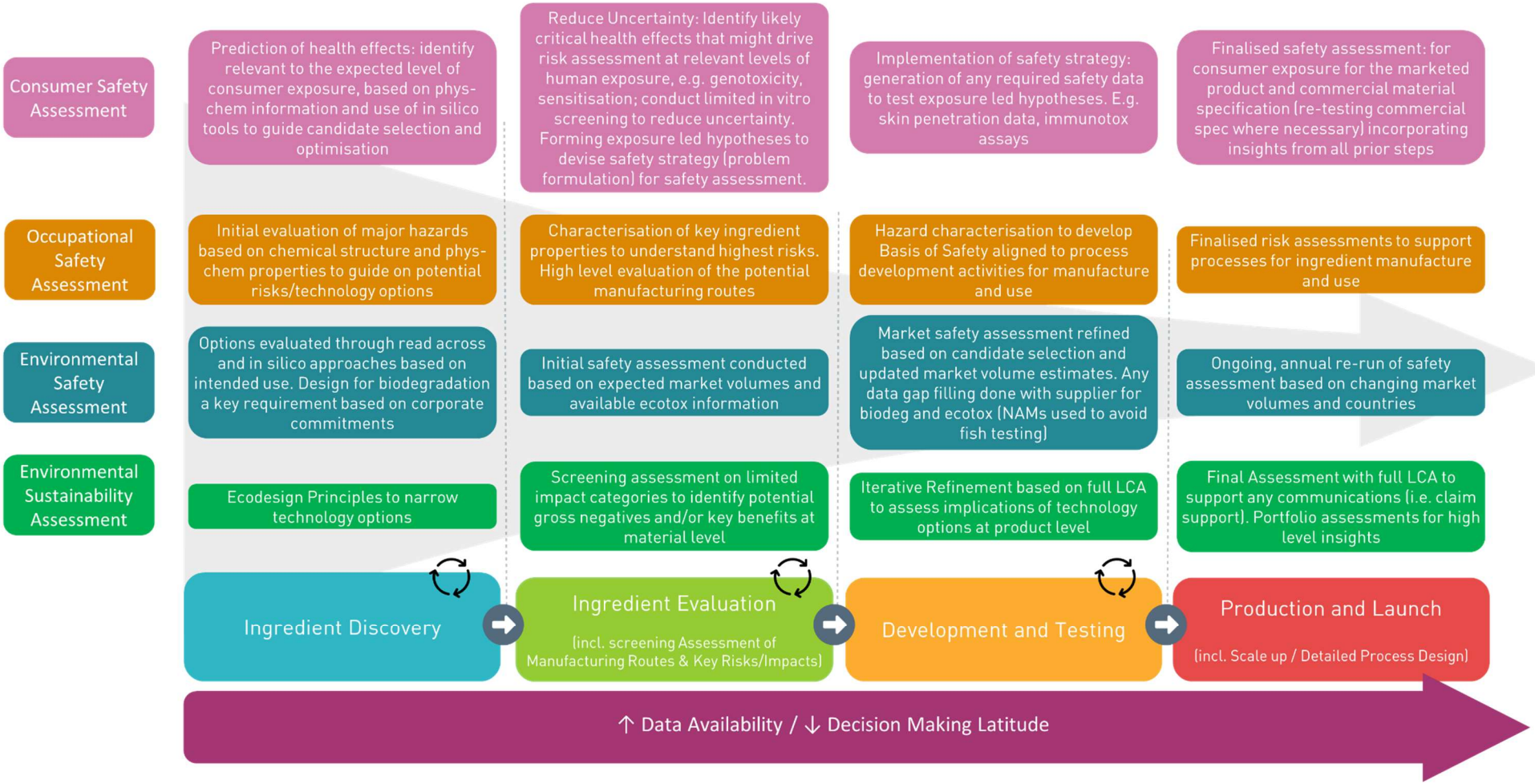

Table 1: Summary of the consumer, occupational and environmental safety and sustainability data and approaches applied at each innovation stage for the evaluation of the biosurfactant for use within a home care cleaning product

INNOVATION STAGE	CONSUMER SAFETY		OCCUPATIONAL SAFETY		ENVIRONMENTAL SAFETY		ENVIRONMENTAL SUSTAINABILITY	
INGREDIENT DISCOVERY	***Data***	***Approach***	***Data***	***Approach***	***Data***	***Approach***	***Data***	***Approach***
Several ingredient options with early-stage supplier information •Evaluation of range of ingredient/ technology options •Preliminary prognosis / screening assessment / in silico predictions of lead technology(ies) •Limited safety & sustainability data	•Surfactant class - read across •Literature on potential immune effects •Production strain •(No data on specific substance)	•In-silico predictions of potential health effects based on expected consumer exposure •Identification of Potential contaminants / residues of concern	•Form & concentration •Surfactant class - read across •Production process •Literature for physical properties e.g. flammability	•Assess for highly hazardous properties •In-silico predictions of potential health effects based on expected worker exposure •Potential contaminants / residuals of concern	•Surfactant class - read across •Bio-degradability data from supplier	•Environmental fate and effects •Estimates of environmental exposure for markets and volumes	•Life cycle stages / production process for material •Feedstock options •Supplier environmental performance claims •(No LCI data)	•Construct process flow •'Rule of thumb' principles / heuristics for qualitative hotspot identification - impacts and life cycle stages •Identify potential risks / benefits and improvement potential
	Conclusions		***Conclusions***		***Conclusions***		***Conclusions***	
	•Not likely to be mutagenic or cause skin sensitisation •Skin and eye irritation is likely to be mild in formulation •Low skin penetration anticipated, therefore potential for systemic toxicity is considered low. *•Data required to support predictions. Potential immune effects need further evaluation - biosurfactant & contaminants*		•No major hazards preventing full scale manufacture expected *•Further hazard characterisation/data needed together with dishwash liquid process and formulation details*		•Biosurfactant is readily biodegradable •Unlikely to be highly ecotoxic •High market volumes expected to be supported *•Refined assessment needed using specific information on biosurfactant and product*		•Reduced exposure to environmental risks (crude oil & PKO) •Low surfactant inclusion levels expected to reduce environmental impacts of product *•Land use and food security considerations require attention*	

INNOVATION STAGE	CONSUMER SAFETY		OCCUPATIONAL SAFETY		ENVIRONMENTAL SAFETY		ENVIRONMENTAL SUSTAINABILITY	
INGREDIENT EVALUATION	***Data***	***Approach***	***Data***	***Approach***	***Data***	***Approach***	***Data***	***Approach***
One / few ingredient options carrying quantitative material and process data (ingredient pilot plant) •Evaluation of lead ingredient/technology option(s) •Identification of significant risks and impacts •Data generation on ingredient performance, safety & sustainability	•Literature for read across data •Chemical Characterisation •In vitro data for genotoxicity and skin sensitisation •In silico predictions of expected metabolites	•Higher-tier in-silico predictions of potential health effects based on refined consumer exposure estimates •Targeted in vitro testing •Assess risk posed by expected contaminants of concern	•Early-stage process design •Initial Toxicological information from consumer safety assessment •Chemical characterisation •Preliminary supplier safety data sheets / information	•Assessment to support process development and design requirements •Potential contaminants / residues of concern	•Expected market volumes •Fate and effects data	•Daphnia and algal acute studies •In silico predictions for fish toxicity e.g. read across, weight of evidence approaches based on MoA •Log K_{ow} and K_{IAM} approaches to estimate biaccumulation	•Pilot plant production data for ingredient - energy & material use •Life cycle inventories / assessments for comparative surfactants	•Quantitative screening LCA assessment of ingredient - limited impact categories (GHGs, water & land use) •Identify key drivers of impacts, possible environmental trade-offs and improvement potential
	Conclusions		***Conclusions***		***Conclusions***		***Conclusions***	
	•Genotoxic carcinogenicity is unlikely •Unlikely to cause skin sensitisation •Not expected to be pathogenic and no viable organism would survive material production *• Need to focus on characterisation of systemic exposure and health effects*		•No major hazards identified from initial toxicological review that result in high risks for workers *•Assessment of potential inhalation and dermal exposures to residual contaminants (proteins, bacteria) in the biosurfactant / formulated product needed.*		•Material is not classified as PBT/vPvB, PMT/vPvM nor Acute or Chronic classes •Prospective safety of the biosurfactant can be assured for current launch plans •Possible *further refinement of the biosurfactant assessment based on final launch plans* *•"Total Tonnage" assessment of other formulation ingredients needed*		•Biosurfactant has higher impact than industry average equivalent surfactant for some of the impact categories. *•Assessment in product formulation required to evaluate impact of low surfactant inclusion levels*	

INNOVATION STAGE	CONSUMER SAFETY		OCCUPATIONAL SAFETY		ENVIRONMENTAL SAFETY		ENVIRONMENTAL SUSTAINABILITY	
DEVELOPMENT & TESTING	***Data***	***Approach***	***Data***	***Approach***	***Data***	***Approach***	***Data***	***Approach***
Commercial specification of Ingredient and product formulation information (product pilot plant) •Refined evaluation of lead ingredient technology option in formulation •Implementation of safety strategy •Data gap filling	•In vitro data for genotoxicity, skin sensitisation, skin absorption and immune effects. •Critical micelle concentration (CMC) for biosurfactant.	•Exposure-led, hypothesis driven safety strategy for local and systemic toxicity. •Characterisation of systemic exposure and health effects •Safety Hypothesis testing in vitro to establish Bioactivity-exposure-ratio (BER)	•Specific form / concentration of ingredient •Chemical/bio-logical characterisation data •Detailed data on existing product manufacturing facility and processes •Residual hazard information •Complete supplier safety data sheets	•Application of inherent safety approaches •Risk assessment for handling ingredient and formulated product •Basis of safety to manage residual risks throughout the whole process	•Incremental volume adjustments for ingredients in the product that are already used within Unilever's portfolio and have been demonstrated to be safe	•Data generation and prospective safety assessment for all ingredients in the product taking a "Total Tonnage" approach	•Formulation data •Value chain process flow information •Life cycle inventories for biosurfactant and other product ingredients / processes •Globally available, spatial land cover data •Production scale-up scenarios: ingredient production & feedstock locations & amounts	•Comparative LCA: new product formulation with biosurfactant vs. existing formulation with non-bio surfactant •LUCI-LCA – high tier prospective spatial modelling considering potential LULUC impacts for scale-up scenarios of bio-based ingredient •GHGs, soil erosion, biodiversity loss, nutrient pollution [human and environmental safety impact categories not applied]
	Conclusions		***Conclusions***		***Conclusions***		***Conclusions***	
	•Found no or negligible exposure via the dermal route leading to favourable margin of safety based on BER. • *Finalisation of the risk assessment, any re-testing required due to scale up to commercial production.*		•Sufficient safety information to be able to characterise worker risks and define suitable process-related risk management measures *•More detailed risk assessments required to confirm all worker safety risks have been addressed* *•Validation of biosurfactant quality/residual levels*		•Demonstrated safety for biosurfactant and other ingredients within the new product *•Check total tonnages & validity of prospective assessments for roll-out plans years 1-3*		•Conditions for improved environmental outcomes established (i.e., % surfactant reduction; feedstock cultivation conditions) •New formulation delivers environmental improvements over existing formulation *•Conduct full LCA if claims anticipated*	

INNOVATION STAGE	CONSUMER SAFETY		OCCUPATIONAL SAFETY		ENVIRONMENTAL SAFETY		ENVIRONMENTAL SUSTAINABILITY	
PRODUCTION & LAUNCH	***Data***	***Approach***	***Data***	***Approach***	***Data***	***Approach***	***Data***	***Approach***
Full-scale production of final formulation with markets & volume targets •Final evaluation of lead ingredient technology option in formulation •Safety and sustainability assessments support market launch • Complete Information and insights from all stages integrated	•Commercial Scale Composition and Consumer exposure scenario locked. •Full in vitro data package now complete with re-testing of commercial spec where necessary.	•Exposure-led, hypothesis driven safety strategy for local and systemic toxicity of commercial specification.	•All hazardous properties defined •Consumer safety data •Handling processes & methods •Inherent safety principles & control measures	•Detailed review of the entire process, potential exposures & controls •Consider manufacturing steps & other workplace activities e.g. cleaning, maintenance, spillages	•Changes in market volumes (prospective / retrospective)	•Annual post-launch monitoring of safety of all ingredients - total tonnage approach •Refinements to the conservative assessments where safety margins are narrowing	•[Data refinements for markets of interest - e.g. transport details / grid mixes]	•[Full LCA* for claims substantiation and ongoing maintenance of claims - tailored to specific markets. N.B. in this instance, not required]
	Conclusions		***Conclusions***		***Conclusions***		***Conclusions***	
	•The biosurfactant and its potential contaminants are non-genotoxic and non-sensitising. •Eye and skin irritation when formulated is mild compared to existing products. •The BER calculated shows a large margin between potential systemic effects and realistic worst case consumer exposure; therefore the surfactant is safe for the intended use		•Detailed risk assessments confirm that all necessary safety measures are in place to manage worker safety risks associated with the new biosurfactant and dishwash liquid product		•Ongoing monitoring of market volumes maintains confidence that additional uses remain safe for the environment. •If safety margins reduce, additional data generation and refinements to assessments •Ultimate option of risk management through restrictions to Unilever use of any materials if safety margins are expected to be exceeded and further refinement of the assessment is not viable		•Environmental benefits not communicated to consumer in this instance so additional work not conducted at this stage	

*'Full' LCA as distinct from 'screening' LCA: typically excludes human and ecotoxicity assessment when applied within Unilever

Acronyms:

K_{ow}	Octanol-water partition coefficient		
K_{IAM}	Immobilised artificial membrane partition co-efficient	PMT/vPvM	Persistent Mobile Toxic/very Persistent very Mobile
MoA	Mode of Action	CMC	Critical Micelle Concentration
PBT/vPvB	Persistent Bioaccumulative Toxic/very Persistent very Bioaccumulative	BER	Bioactivity Exposure Ratio

Part II: Unilever reflections on the JRC Safe and Sustainable by design (SSbD) framework

We have reviewed the JRC Safe and Sustainable by Design (SSbD) framework (Caldeira et al, 2022), including the accompanying JRC case study (Caldeira et al, 2023), in the context of Unilever's internal assessment approaches (see Part I). Based on this review, we provide a downstream user point of view and recommendations for further development of the JRC SSbD framework. We recognise the aspiration of the framework as a mechanism to help drive competitive, sustainable growth within the EU and we provide our reflections in this context. Our observations are grounded in deep technical understanding of both safety and sustainability science, data and tools (current and emerging) as well as knowledge of the practicalities of consumer product innovation, but we recognise varied levels of capability across industry when providing our recommendations.

Conceptual framing

The SSbD framework comprehensively references a range of conceptual and assessment approaches, framing the ambition for **absolute safety and sustainability**. Although practical implications to this framing are acknowledged in the JRC report, we would go further and outline more fundamental challenges. The notion of 'absolute safety' or 'absolute sustainability' for defined uses of a specific chemical, is simply not a viable / desirable ambition.

Absolute safety, when defined by hazard alone and intended to account for all potential uses will be undesirable, even if possible to achieve. It would inevitably result in discarding many materials with moderate or even higher intrinsic hazard, which can be used safely for well-defined applications. Consequently, regrettable substitution and a stifling of advanced chemical and material discovery is likely, as chemicals with lower intrinsic hazard profiles are favoured despite potential trade-offs, such as higher environmental impacts. We believe that safety should be assessed based on hazard and exposure and there may be examples of new and existing chemicals with greater hazards that can be managed through demonstrated for well-defined and controlled exposures.

Mainstream assessment of **absolute sustainability**, defined by planetary boundaries, for *specific product uses* is not yet possible. In principle the idea is appealing, but the real added value would likely be to support evaluation of innovation strategies or themes (e.g. biosurfactants as a class rather than an individual biosurfactant) rooted in prospective (not consequential) scenario assessment, rather than *routine* assessment of individual chemicals for specific uses. The latter would be practically impossible to achieve given the dynamic temporal and spatial nature of allocating shares of safe operating space. There are various nascent attempts in the literature[5] to develop PB-LCA methodologies (some of which co-developed / demonstrated by us[6]) that might support an ambition

[5] Bjørn A, et al. 2020. Environmental Research Letters, 15: 083001.

[6] Bjørn, A. et al. 2020. Int J Life Cycle Assess 25, pp 2241–2254.

Bjørn A, et al. 2020. Science of the Total Environment, 136813.

of absolute assessment of innovation themes, but we anticipate an intensive research agenda over the medium-long term (~10 years) to achieve robust and consensus driven science in PB-LCA.

Staged assessments, methods and data availability

The framework is intended for the assessment of both **chemicals and materials**; the definition of materials needs further clarification as the current broad definition substantially expands the scope of application. Our review of the assessment framework considers chemicals.

The **'Stage Gate' process** is correctly identified as a common approach to innovation across industry and has been used to inform a step-wise approach to assessment in the SSbD framework. However, the steps are articulated based on the safety and sustainability dimension only and not also the innovation stages. Whilst we assume the intent is for flexibility in conducting the steps iteratively and in parallel, it would be helpful if the staged assessment were more explicitly aligned to innovation stages. We believe this would encourage greater adoption within industry as implementation within existing processes would be more tangible.

For example, the framework is clear that the assessment is not sequential, but greater recognition that each step can be assessed in parallel to others with a progressive level of depth through innovation could be of benefit. With such an approach, the output of the assessment built at stages throughout innovation could be made available to internal company and external stakeholders involved or interested in the design of the new material making it clear that it is an interim assessment that communicates the findings so far, conclusions that have been drawn and elements that are still to be assessed (e.g. a focus on priority hazard endpoints and whether these have been assessed using screening or more definitive data).

When considering the **methods and approaches** indicated for the safety and sustainability assessment of chemicals, we support the use of **non-animal New Approach Methodologies (or NAMs)** (i.e. the intent behind Annex 2 and Table A2 of the JRC case study report). We strongly believe that the SSbD framework should not be a driver for additional animal testing. Instead, all existing data should be utilised as far as possible, either on the chemical itself or read-cross from similar chemicals, and non-animal NAMs should be used wherever required to assess safety. Further co-development of a toolbox of non-animal NAMs across stakeholders that can be applied at various innovation stages should be a priority. For early innovation stages, assessment should be focused on the most relevant safety elements of the intended use and associated exposures, rather than attempting to assess against every hazard endpoint. Flexibility should be built into the framework to allow the use of non-animal NAMs such as Bioactivity Exposure Ratio (BER) which, although not designed to meet the

Bjørn A, et al. 2020. Ecological Indicators, 110: 105865.

Bjørn A, et al. 2019. Science of the Total Environment, 696, 133964.

Ryberg WR, et al. 2018. Science of the Total Environment, 634, 1406-1416.

requirements of CLP (i.e. needed for step 1), have been shown to be valuable in a screening assessment for human safety[7].

Whilst we are strong advocates of environmental **Life Cycle Assessment (LCA),** we believe that evaluation of chemicals structured around innovation stages also calls for deployment of rule-bases / 'rules of thumb' / eco-design principles (Figure 1 & Table 1) that embed qualitative **Life Cycle Thinking** in early innovation. **LCA screening** can be performed when data availability improves in subsequent innovation stages moving to more comprehensive / 'full' LCA. There should be flexibility to use '**high-tier' LCA** where warranted, for example, existing spatial LCA methods such as LUCI-LCA[8] or new methodological advancements as they become available. Even when conducting comprehensive LCA (e.g. to support product launch and potential claims) we would question the need for PEF-LCA on all occasions; assessment of 16 impact categories may not be relevant for all innovations, considering both materiality and the maturity of characterisation factors. Usetox indicators in LCA that attempt to account for human and environmental toxicity impacts may not be the most material factors within decision making for chemicals where their direct exposure to humans and the environment occur through use. In addition, there is a challenge to implement non-animal NAMS in a Usetox framework in order to apply Usetox factors for assessment of chemicals in sectors / brands committed to non-animal testing. These safety considerations, will be better assessed in steps 2 and 3 of the SSbD framework, based on non-animal NAMs and an understanding of human and environment exposure in manufacture and use.

We also note reference to **Social LCA** in the SSbD framework, which raises some concerns. LCA is a 'hard systems' methodology focused on the analysis of value chain processes, whereas social impacts are the product of 'soft systems', generally governed by organisational values, policies, and behaviour[9]. Social risks and impacts may best be managed via soft system governance procedures (e.g. responsible sourcing policies). These generally operate at a corporate rather than a material / product innovation level.

When considering the **availability of data required** for safety and sustainability assessments particularly at early stages of innovation, we highlight several areas of challenge, as follows.

For safety, alongside the challenges of availability of hazard data which can partly be addressed by building the assessment through innovation stages, focus on priority endpoints and use of non-animal NAMs, availability of suitably described consumer, worker and environmental **exposure scenarios** are key to the assessments needed in steps 2 and 3. Such exposure scenarios are not always well described within screening level tools such as ECETOC TRA and do not necessarily drive SSbD improvements in development activities. More refined exposure scenarios could be created at the sector level and made available for use within a future SSbD toolbox. In prioritising which exposure scenarios are needed, consideration could be made to key hotspots within the value chain for human and environmental safety. For example, within cosmetics or household cleaning products, the use phase

[7] Paul Friedman et al Toxicol Sci. 2020 Jan 1; 173(1): 202–225

[8] Chaplin-Kramer, R. et al. 2017. Nat Commun 8, 15065.

[9] https://openresearch.surrey.ac.uk/esploro/outputs/doctoral/Sustainable-Food-Supply-Chains-Volume-1/99515427402346 (Chapter 4)

is often the most important for human and environmental safety, especially when worker exposures during product manufacture are strictly controlled.

For sustainability, availability of **Life Cycle inventory data** is often limited even for existing chemicals and materials (those to which new chemicals / materials will likely be compared). For existing chemicals and materials, we recommend exploring the generation and availability of more LCI data e.g. through sector-based initiatives to generate datasets that reflect potentially different production technologies and feedstocks, and regionalised for main production locations. By ensuring a shared responsibility for data sharing across the supply chain, these can then be made available for use (with possible refinement by users to generate company-specific datasets) to provide comparator information against which new chemicals and materials can be compared. Better approaches to simulate or predict data inventories (with quantified uncertainty related to TRL) are also needed for assessment of new chemicals and materials. This could include further research on how to conduct prospective LCAs in an insightful way, how to quantify and account for the uncertainty linked to studies of immature technologies, or more innovative techniques such as new digital tools for gap filling of inventories and predictive optimisation of novel processes.

Accounting for trade-offs

As it is unlikely that a SSbD assessment for a new chemical will demonstrate improvements against an existing chemical in all aspects, one important aspect of any SSbD assessment will be dealing with trade-offs. We do not believe that safety in use combining hazard and exposure should be traded-off. However, trade-offs could be applied between sustainability and hazard classes (specifically in favour of sustainability assuming hazards can be managed). For example, it may be advantageous to develop a chemical with a higher hazard that can be safely managed through production and well-defined use if it delivers substantial sustainability benefits versus another chemical which has low hazard but does not deliver the same benefits.

We believe that trade-offs between environmental impact categories when applied at a total production (all chemicals / materials or even material goods) level should be avoided, especially for impact categories known to be critical for Earth System (ES) regulation. However, within the SSbD sustainability assessment framework, various of the 16 LCA impact categories are not considered to be ES regulating and there are considerable conceptual challenges with the inherent idea that avoiding trade-offs between impact categories on an individual chemical / material basis is possible. For this reason, trade-offs within the sustainability assessment should be entertained and consideration on how to best deal with these is needed. We believe this should focus on the sustainability aspects most material to the chemical, supply chain and use in question, and should recognise varying degrees of confidence in the estimated impacts, reflecting differing levels of maturity of impact characterisation.

Priority, or most material, safety and sustainability dimensions can be set based on the specific concerns or needs of value chain stakeholders. If improvement against these dimensions is achieved through innovation, then the focus should be to ensure additional or priority safety risks or sustainability impacts are not introduced that cannot be managed (e.g. a hazard to consumer safety

that cannot be managed through product format or formulation or an occupational hazard that cannot be controlled by protective equipment to minimise exposure).

It is through approaches like this that we believe more progress will be made towards safe and more sustainable chemicals versus disincentivising chemicals that may be better in key areas but not across all areas.

Scoring approaches

When considering scoring, further reflection is needed on the level at which scoring is applied. An overall scoring system captured in one overall rating removes key details needed to make a judgement on the acceptability of the inevitable trade-offs, and risks becoming overly reductive. For this reason we would recommend that aggregate scoring is most appropriate within each SSbD step, and that aggregate scoring across steps (safety and sustainability dimensions) is best avoided. In addition, aggregate scoring of env sustainability would ideally facilitate application of EU harmonised ecolabelling approaches, for instances where such consumer communication is desirable.

The granularity of scoring even within steps may require further consideration. For example, reliance on approaches such as RCRs (Risk Characterisation Ratios) may give a false impression of the comparative safety of chemicals. RCRs can be a product of the level of refinement or available data within an assessment where data rich substances may benefit from a more refined assessment with better RCRs than a data poor substance that needs to rely on a more conservative assessment (e.g. with higher Assessment Factors).

In the early stages of R&D activity, with data usually limited, qualitative assessment approaches for scoring that look at the potential safety and sustainability concerns may offer a simpler and more pragmatic way to identify the highest potential risks. This would provide a simpler way to review alternative technologies or processes and help in prioritising areas where further hazard characterisation, data generation or some aspects of re-design are required.

In addition, consideration will need to be given on the communication of any overall SSbD score. As the assessment conducted will be specific to certain value chains and uses, these would need to be communicated carefully to avoid an SSbD score being applied to other value chains or uses of the given chemical.

Summary of recommendations for further development of the SSbD framework

Our belief is that sustainable product innovation can only be truly embedded in company operations if an enabling environment is offered both by the external policy context (e.g. as per the objectives of the European Green Deal) and individual business strategies. Company vision, strategy and culture are essential: a harmonised assessment framework such as SSbD may help to embed safe and sustainable design considerations at an operational level, offering a toolbox for evaluating innovation choices and examining potential trade-offs, but will only be effective if company culture is conducive. Such a framework is likely to be most effective if aligned to the existing stage gate innovation process, with explicit acknowledgement of the need for iterative and parallel assessment of both safety and sustainability elements that accounts for data availability and methodological feasibility at each stage.

We argue that the concept of “absolute” safety (as defined by hazard alone) or sustainability (when applied to individual chemicals and associated uses) as described in the report is not achievable in the short term and may not be desirable. For example, safety should be assessed based on hazard and exposure (as in steps 2 and 3) and there may be examples of new chemicals with greater hazards that can be managed through exposure/use and deliver significant sustainability benefits. Disincentivising such chemicals with potential benefits to society would be counter-productive to the objectives of the European Green Deal. We believe that how the framework deals with trade-offs will be key in how the framework supports progress against the transition of chemical industry towards safe and more sustainable chemicals. Expecting new chemicals to have an improved profile against all hazard endpoints (regardless of how these can be managed through production, use and disposal) and all sustainability impact categories may prevent the SSbD concept being adopted or it driving incremental improvements.

An SSbD assessment toolbox should consider both qualitative and quantitative assessment approaches and we recommend that further developments of the SSbD framework are focused on:

1. pre-assessment / early-stage screening (e.g. rule-bases, question-sets etc.) especially using non-animal NAMs such as BER, even if they have not been designed to meet current CLP requirements and

2. sector-based approaches to define generic exposure scenarios or LCI data.

Availability of such approaches and information would help to guide innovation in future-looking advanced chemicals and materials, whilst minimising the economic burden for industry (and ultimately consumers) and the risk of precluding SMEs from implementing SSbD. That said, review and further development of an SSbD toolbox beyond such tier 1 assessment techniques is likely required, and ongoing flexibility of approaches will be needed with mechanisms to accommodate new safety and sustainability assessment approaches.

Annex 1: Details of the consumer, occupational and environmental safety and sustainability data and approaches applied at each innovation stage for the evaluation of the biosurfactant for use within a home care cleaning product.

Ingredient Discovery

This stage of innovation is focussed on the identification of alternative surfactant candidates using biobased sources of carbon. Selection considerations include desired functional benefits such as enhanced skin mildness, superior cleaning performance, robust performance in variable water conditions and superior biodegradability. R&D teams scout for and/or invent potential materials, evaluating these for performance. Lead candidates are shared with safety and sustainability scientists. At this early stage of innovation, it is common for the several options being considered to have limited safety & sustainability data, meaning it is not possible to conduct full prospective, quantitative assessments. Instead, preliminary prognoses on potential safety and sustainability considerations for the options are provided. Further investigation and refinement of safety and sustainability considerations occurs throughout the innovation process for the selection of lead candidates and based on the expected use in products.

Consumer Safety:

During this stage of innovation, consumer safety prognoses are written based on information that is readily available, such as physical-chemical parameters and public-domain literature, for materials with similar chemical structures. Preliminary exposure estimates are carried out based on expected inclusion levels and potential product types to identify likely routes of exposure to establish levels of local and systemic (internal) exposure to consumers. These exposure estimates give an initial indication of the plausibility of using exposure based waiving techniques to support safety (or indicate a high chance of favourable outcome in subsequent safety testing) and, if levels exceed exposure-based waving thresholds, this knowledge helps to prioritise which aspects of local and systemic toxicity for further investigation.

In silico predictions of biological activity are often used at this stage. These Quantitative Structure Activity Relationship (QSAR) models provide mechanistic insights and highlight any structural components of concern. Emphasis is given to the plausibility of key molecular initiating events that might be associated with the novel surfactant causing DNA damage and mutation, as a precursor for carcinogenicity; as well as the ability to covalently bind (adduct) to peptides, as a precursor to skin sensitisation (Type IV).

The presence of residuals (reactive species, proteins, processing aids, monomers etc) of concern is also considered for early identification of potential hazards and the need for specific exposure characterisation. In the case of a biosurfactant produced through microbiological fermentation, consideration is made for the microbial implications on the produced biosurfactant which includes but is not limited to characterisation of the presence of pathogenic strain and potential by-products due to normal metabolism, such as formation of bacterial toxins and presence of residual viable pathogenic organisms. Any residuals of concern identified are shared with the innovation scientists to allow for better characterisation, bearing in mind that this may vary between the lab-scale and the scaled up commercial process.

The consumer safety prognosis is shared with the innovation scientists to guide candidate selection and optimisation of the design of the material or synthesis/fermentation process.

Illustration through the biosurfactant example:

Objective/Scope of Assessment: Preliminary Assessment of technology, primarily based on screening tools.

- In silico prediction of potential health effects and key events based on expected consumer exposure to the surfactant
- Understanding of potential contaminants and residues of concern.
- Limited literature searching for potential sources of read-across data and material class health effects

Data/information available:

- No Existing Data on substance
- Read across data for similar glycolipid surfactants
- Literature on potential immune effects
- In silico predictions of genotoxicity, protein adducts and potential toxic modes of action.
- Information on production strain indicates lack of pathogenicity

Key questions and considerations and major uncertainties:

- Can bacterial endotoxin levels be characterised?

Conclusion: Not likely to be mutagenic or cause skin sensitisation. Early surfactant efficacy data and read-across suggest skin and eye irritation is likely to be mild in formulation; however, concentrated surfactants are often associated with skin and eye irritation/damage. Immune effects require further evaluation, both of the biosurfactant itself and contaminants (e.g. protein, endotoxin). Skin penetration potential anticipated to be low and likely to be rapidly metabolised. Skin absorption data will need to be refined.

Occupational Safety:

Many different surfactants are available that have been widely used over many years with their key hazards, physical and chemical properties well understood. However, as the biosurfactant will be manufactured via a completely different process route, limited information is available on the full chemical characterisation of the material(s). The primary considerations for the initial evaluation are based on a qualitative assessment of new hazards that could be introduced by the change in manufacturing technology and the potential significance of those hazards.

Further development work would prioritise the hazard assessment to improve the understanding of the most hazardous properties and, where possible, removing those biosurfactant and technology options that present any major risks.

Illustration through the biosurfactant example:

Objective/Scope of Assessment: Preliminary assessment of lead biosurfactant candidates to identify and provide an initial assessment on any potential highly hazardous properties

- In silico prediction of potential health effects based on expected occupational exposures to the surfactant
- Understanding of potential contaminants and residues of concern

- Literature searching for potential sources of read-across data and understanding of physical properties for similar surfactants (e.g. flammability data)

Data/information available:

- Expected form/concentration of the material, available information from the supplier
- Structural similarities and read across to existing surfactants of similar hydrocarbon chain length, form and structure to provide a good estimate of some of the key process and occupational safety hazards
- Application of relevant/available toxicological information generated to support the consumer safety assessment applied to worker exposure scenarios (focus on high risks)
- Information from the supplier on the production process for the new biosurfactant to identify potential contaminants and their associated risks for workers

Key questions and considerations and major uncertainties:

- Presence/level of chemical and biological contaminants and their impacts on manufacturing and worker safety risks
- In partnership with the supplier, identify any additional toxicological information needed for worker exposures that might not be available or needed for the consumer safety assessment

Conclusion: Based on the initial analysis, major hazards that would prevent the technology progressing to full scale manufacture are not expected though further work is required to fully characterise potential risks from residuals produced or remaining in the biosurfactant (e.g. proteins, bacteria, by-products etc.) and their potential to pose any risks to workers.

Environmental Safety:

At this early stage of innovation empirical information on the environmental fate or effects is often unavailable, especially when exploring novel chemicals. Expert knowledge, *in silico* tools and any available existing knowledge on similar chemicals will be used to form an early prognosis. When evaluating new surfactants, information can be used from the extensive study of different surfactant classes over the last 40+ years due to their high volume and wide dispersive use. In addition, ensuring any new surfactant meets a high standard of biodegradability is an essential design attribute for any candidate to progress through the innovation process. This condition reflects regulatory requirements in the EU as well as Unilever corporate requirements for the surfactants used in all Unilever products, in all markets. Consequently, each lead candidate is assessed using any existing data, new testing completed by the supplier, or read-across with similar surfactants or classes.

Based on available information, an environmental safety prognosis can be provided assuming representative market volumes taken from the innovation business case.

Illustration through the biosurfactant example:

Objective/Scope of Assessment: Preliminary Assessment of technology, primarily based on screening tools and early information on potential use in the market.

- Environmental fate and effects screening assessment based on available information from the supplier, *in silico* predictions, expert knowledge or read-across to similar chemicals or classes.
- Early estimates of environmental exposure based on representative market countries and volumes within the innovation business case

Data/information available:

- Information on surfactant options being pursued and their surfactant classes where read-across data can be used
- Biodegradability information conducted by the supplier due to regulatory requirements in the EU for surfactants under the Detergents Regulation.

Key Questions and considerations:

- Confirmation of environmental safety profile based upon the surfactant class
- Understanding fish toxicity without conducting new animal testing

Conclusion: Early assessment based on available information shows that the biosurfactant is readily biodegradable as necessary to meet EU regulations for use as a surfactant in cleaning products. Chemical class data would suggest the biosurfactant is unlikely to be highly ecotoxic. Based on representative use scenarios and other similar surfactants, high market volumes are expected to be supported.

Environmental Sustainability:

Due to limited data availability at this early stage of innovation, it is difficult to quantify the potential environmental impacts of different options. Yet, technology candidates can be evaluated using sustainable design principles and heuristics, focused on aspects such as feedstock origin & availability, material conversion ratios and technology efficiencies, by/co-product identification, and in-formulation efficacy (implications for dose / functional unit). This enables a qualitative evaluation of life cycle stages and identification of those that may signal potentially high / low environmental impacts as well as possible optimisation aspects for further consideration.

Illustration through the biosurfactant example:

Objective/Scope of Assessment: Preliminary Assessment of technology, based on principle only.

- Qualitative preliminary assessment flagging potential environmental sustainability risks/hotspots or benefits (relative to existing comparators)
- Assessment principles based on high-level, 'rule-of-thumb' type approaches for key focus areas

Data/information available:

- Information on surfactant options being pursued
- Qualitative information from the supplier(s) on the production process / life cycle stages for the new biosurfactant as well as feedstock options
- Environmental performance claims and potential benefits (unquantified) from supplier(s)
- No quantitative activity / LCI data

Key questions and considerations:

- Potential benefits due to diversification of workhorse ingredient and feedstock, such as increased resilience
- Risks and impacts of potential feedstock/s: biobased – avoidance of virgin fossil carbon (as compared to conventional surfactants) but impacts of agricultural feedstocks not guaranteed to be lower than fossil sources (GHGs, water, biodiversity). Land use and food security considerations.

- Efficacy: Enhanced cleaning performance – potential to reduce surfactant use in-formulation
- Novel biosurfactant: Low Technology Readiness Level – potential for further production efficiencies when scaling

Conclusion: Quantitative assessment precluded by lack of data. Biosurfactants present an interesting alternative to those derived from crude oil or PKO, potentially reducing exposure to sustainability issues and reducing environmental impacts. Potential for improved product efficacy or the opportunity to reduce surfactant inclusion levels whilst maintaining product performance could also provide important advantage. However, novel biosurfactants are produced from sugar feedstocks (used to feed the bacteria). Further investigation of source regions and land use implications is recommended. A considerable amount of energy is also required for the microorganisms to grow – energy sources will be important for overall sustainability. Preliminary assessment of material suggests potential sustainability benefits, but further assessment is required.

Ingredient Evaluation

Following the Ingredient Discovery stage, in which a range of ingredient options are evaluated, the lead candidate is taken forward into the Ingredient Evaluation phase. During this phase, focussed work is conducted to establish the specific attributes or functionality of the ingredient relative to that defined in the original innovation brief (e.g. enhanced skin mildness, biodegradability, etc). This phase sees a step up in investment in generating the data necessary to assess ingredient performance alongside safety and sustainability. This data generation and subsequent evaluation is focussed on the most significant potential risks or impacts anticipated by the expected end use and available data. As with the Ingredient Discovery phase, key information regarding final concentration in product or market volumes would only be estimated. In addition, since material specification at pilot scale may not yet be finalised, studies and data generation are likely to be aimed at reducing key uncertainties (and may need to be repeated on the final commercial material). Therefore, complete information on the safety and sustainability profile of the lead candidate will not be available, meaning a comprehensive evaluation would not be possible at this stage.

Consumer Safety:

Although a commercial product formulation would not yet be locked, further calculations would be done at this stage to estimate consumer exposure to the biosurfactant (and residuals of concern) based on the predicted product proposition. These calculations are typically conservative in nature and are based on available physiological data for the relevant population and habits and practices data. Based on the outcome of these calculations a decision is made as to whether exposure-based waiving, such as Threshold of Toxicological Concern (TTC, described by Kroes *et al., 2005*[10]) or Dermal Sensitisation Threshold (DST, described by Safford, 2008[11]), is applicable for the proposed use of the biosurfactant.

As a lead candidate has been identified at this stage, a more thorough literature search is carried out. The information gathered serves to further identify likely hazards associated with the lead material but also to identify any potential candidate materials for a read-across assessment.

[10] R. Kroes et al. 2005. Toxicological Sciences, 86(2) 2, pp 226–230.

[11] R.J. Safford. 2008. Regulatory Toxicology and Pharmacology, 51(2), pp 195-200.

Potential key health effects are identified based on *in silico* predictions and any knowledge from the literature or chemistry of the lead candidate and prioritised for data generation to reduce uncertainties in the assessment. Often, *in vitro* data generation for genotoxicity and skin sensitisation (such as the direct peptide reactivity assay) are carried out at this stage to reduce uncertainty regarding the critical health effects.

Considering what is known about the biosurfactant at this stage, a problem formulation is carried out to form an exposure led safety strategy to ultimately support the safe use of the biosurfactant in consumer products. In the case of a biosurfactant included in a hand dishwash product, it is key to characterise the dermal absorption potential (as the primary route of consumer exposure) and critical micellar concentration (as a benchmark to currently used surfactants), as well as potential to interact with the immune system based on evidence from similar substances in the literature.

Illustration through the biosurfactant example:

Objective/Scope of Assessment: More detailed screening to reduce uncertainties in the assessment.

- Higher tier in silico prediction of potential health effects and key events based on expected consumer exposure to the surfactant, including predictions of principal metabolites
- Targeted *in vitro* testing following up on early *in silico* screening output to reduce uncertainties
- Analytical characterisation of potential contaminants and residues of concern and understanding of the likely impact of scale up on the material profile
- Comprehensive literature searching for potential sources of read-across data

Data/information available:

(In addition to the *in silico* predictions during the Ingredient Discovery Phase)

- *In vitro* genotoxicity data generated to showing lack of genotoxicity, hence genotoxic carcinogenicity is unlikely
- *In vitro* peptide reactivity data generated suggesting the material is unlikely to adduct to protein, hence, the biosurfactant is considered unlikely to cause skin sensitisation.
- Predictions of metabolism suggest likely metabolites would be sugars and fatty acids found in nature and hence of low concern.
- Although not expected to be pathogenic, could be considered an opportunistic pathogen; however, no viable organism would survive material production.

Key questions and considerations and major uncertainties:

- As refined exposure calculations confirm exposure-based waiving is out of scope for systemic effects, skin absorption will be critical for assessing systemic exposure following dermal contact
- Bacterial endotoxin levels in commercial specification need to be measured.
- Need to explore literature reports of immune effects, understand systemic exposure in the context of skin absorption, and characterise potential systemic health effects.
- Gain better understanding of local effects; whilst skin sensitisation is unlikely, need to confirm the expected mildness of the surfactant in *in vitro* assays to build understanding of other local effects i.e. skin/eye irritation/corrosion.

Conclusion: Key *in silico* alerts regarding genotoxiciy and skin sensitisation have been addressed by generating *in vitro* data. Assessment goal during the development and testing stage to focus on characterisation of systemic exposure and effects.

Occupational Safety:

At this stage, it is still possible to influence multiple process design factors (ingredients, feedstocks and process routes) that can have a strong influence on the potential hazards. The focus will be on those hazards that could pose significant safety risks to workers or require significant additional costs or complexity to implement in Unilever manufacturing sites. An early understanding of these risks can then be used to influence the development activities for the biosurfactant and its associated manufacturing process.

Wherever possible, technology selection that eliminates potential high hazards should be prioritised. For example, the selection of strains of source bacteria for the fermentation reaction that are not pathogenic to humans and are not expected to produce very hazardous by-products. Where elimination of such bacteria is not feasible, consideration would need to focus on the need for downstream processing steps to remove or inactivate any residual bacteria that may cause harm.

Illustration through the biosurfactant example:

Objective/Scope of Assessment: Preliminary assessment to support process development and design requirements for manufacture of the consumer product

- More detailed toxicological information to refine the risk assessment view for the expected worker exposures.
- Understanding of potential contaminants and residues of concern.
- Implications for process design and any hazard elimination / reduction measures that may be required.

Data/information available:

- Early-stage process design and expected inclusion levels for the consumer product incorporating the biosurfactant.
- Application of relevant/available toxicological information generated to support the consumer safety assessment to worker exposure scenarios.
- More quantitative/analytical data on potential contaminants/residuals in the biosurfactant
- Preliminary supplier safety data sheets to enable small scale sourcing of the biosurfactant for experimental/product formulation development work.

Key questions and considerations:

- The potential source organisms/bacteria, feedstocks, media materials and fermentation conditions/yield will provide some early indication on possible residuals/contaminants, their levels, their hazard potential, and any further toxicological and microbiological safety assessments that may be required to assess the potential hazards and the risks they pose.
- The potential biosurfactant processing routes and the influence on potential hazards
- Potential process risks from the biosurfactant physical/chemical properties and worker exposure risks for various process handling and design options for incorporation of the biosurfactant into the existing manufacturing process for the consumer products.

Conclusion: No major risks identified though further data is needed to fully characterise the biosurfactant and residual components produced by the new process. Key areas to address will be

potential inhalation and dermal exposures to the biosurfactant and associated residuals in the biosurfactant and fully formulated consumer products.

Environmental Safety:

As a lead candidate is identified, a prospective environmental safety assessment is conducted based upon available fate or effects data and refined market volume estimates based on the project business case. An EUSES aligned environmental safety assessment model developed for global market countries is used for this prospective assessment. Conservative assumptions are taken when data are lacking but should safety not be demonstrated then further data can be generated to refine the assessment. In the case of ecotoxicity data, non-animal NAMs are used to evaluate fish toxicity or bioaccumulation. This could be reliance on *in silico* predictions including fish PBPK models, read across, weight of evidence approaches based on mode of action (MoA) to determine if fish could be the most sensitive species, or in vitro tests such as fish gill cell line assays or fish S9 or hepatocytes assays for bioaccumulation.

Illustration through the biosurfactant example:

Objective/Scope of Assessment: Generation or sourcing environmental data on lead candidate. Prospective environmental safety assessment for marketing strategy.

- Data generation of the lead candidate by the supplier for Daphnia and algal toxicity.
- Comparison of data against other surfactants of similar class.
- Strategy to evaluate fish toxicity without conducting animal testing.
- Bioaccumulation and mobility estimates made based on read across to similar surfactants.

Data/information available:

- Confirmed pass within an OECD 301 Ready biodegradation study with >90% biodegradation observed in 28 days.
- Daphnia and algal acute studies show low toxicity with EC_{50}s >100mg/l. Based on expected non-specific membrane-based narcosis MoA with Acute:Chronic ratios (ACRs) less than 10, high chronic toxicity is not likely.
- Using a class-based assessment reading across from other surfactants and using MoA arguments, fish are expected to show similar acute and chronic toxicity to Daphnia and algae.
- Measured log K_{ow} of the fully ionised form at environmentally relevant pH show that the material has no potential to bioaccumulate. Although it is recognised that low K_{ow} may not always be the best predictor of bioaccumulation potential for surfactants with alternative methods such as membrane-water partition (K_{mw}) using immobilised artificial membranes to derive K_{IAM} coefficients being more representative, a weight of evidence approach taking all available information known strongly indicates a low bioaccumulation potential.

Key questions and considerations and major uncertainties:

- Further refinement of the prospective safety assessment based on expected volumes and market countries in years 1 to 3 post launch as the project business case evolves through innovation process.

Conclusion: Available information on the lead candidate, as well as read across from similar class of surfactants, show that the material is not hazardous to the environment neither PBT/vPvB nor

PMT/vPvM and will not be environmentally classified. Similarly, using expected market volumes, prospective safety can be assured for launch plans.

Environmental Sustainability:

At this stage, greater data availability will support quantitative screening-type assessments, helping to confirm environmental impacts and benefits of the biosurfactant selected as lead candidate relative to existing technologies in use (i.e. petrochemical and oleo surfactants) at material level. At this stage, attributional LCA approaches are employed, either descriptive or prospective. Consequential assessment is not favoured due to the difficulty in anticipating physical and monetary causalities related to technology change and thus the high degree of uncertainty that is generally associated with modelling assumptions and assessment results.

Illustration through the biosurfactant example:

Objective/Scope of Assessment: Screening comparative assessment at material level – novel biosurfactant vs petrochemical and oleo surfactants – based on preliminary information to inform directional view, on a limited set of impacts (e.g. climate change, water use and land use). Scope of assessment determined with reference to findings of the previous step (potential benefits/gross negatives).

Data/information available:

- Production data provided by supplier: supplier pilot plant data for ingredient production (direct measurements of energy and material use.

Key questions and considerations:

- Biosurfactant has higher impact than industry average equivalent surfactant for some of the impact categories. Assessment in product formulation required.

Conclusion: Assessment provides key insights into drivers of impact and potential environmental trade-offs when using the biosurfactant vs traditional surfactants. Need for further assessments to consider product reformulation in case of increased efficiency (i.e., decreased inclusion levels of surfactant in product).

Development and Testing

The development and testing phase is where ingredient evaluation is taken into a whole formulation or product design context. Small to larger scale consumer tests may be conducted requiring full product consumer safety assessments before any product is placed into the hands of a consumer. More detailed process development work is carried out to progress the product manufacturing process design, including the manufacturing requirements for scale up and full-scale manufacture, addressing any product quality and stability issues. This often requires use of pilot plant scale processes and full-scale main plant trails to confirm or validate the process and formulation design.

Consumer Safety:

The safety strategy devised during Ingredient Evaluation would now be deployed in a tiered manner. The strategy will have been developed to ensure the biological coverage of the tools used to characterise the potential health effects of the material. Data are generated in a prioritised, exposure

led and hypothesis driven manner. Building on any initial screening studies from the 'Ingredient Evaluation' phase, key considerations will be to:

- generate data to refine the systemic exposure to the biosurfactant (skin penetration) and potential metabolites;
- complete genotoxicity study data package if required;
- establish a suitable 'point of departure' to characterise relevant health hazards (immunotoxicity, skin allergy, systemic toxicity, etc.).

To be protective for systemic health effects, the *in vitro* hazard characterisation is assessed in the context of the conservative consumer exposure, in order to derive a bioactivity-exposure-ratio (BER). This is analogous to the 'Margin of Safety' between the exposure at a point of departure in animal studies[12]. As outlined in Middleton et al. 2022, an acceptable BER margin of safety when based on biological perturbations (which is not necessarily linked to toxicity / adverse outcome) could lead to excessive conservatism and will likely need to be judged on case-by-case basis in the context of uncertainty throughout the assessment. However, it is possible to conclude that the proposed use of the biosurfactant is protective of any health effect. In cases when the BER gives a small margin of safety, further characterisation and refinement can be done using higher tier tools to further explore biological effect and the consumer exposure.

Once the expected commercial specification of the biosurfactant is known, as scale up and main plant trials progress, analytical data on the biosurfactant purity and residual contaminants informs the safety assessment and is carried out in a similar manner as discussed in prior steps (using existing data, EBW, read across etc.).

Illustration through the biosurfactant example:

Objective/Scope of Assessment: More detailed screening to reduce uncertainties in the assessment.

- Exposure assessments for local (site of contact) and systemic.
- Understanding of metabolic fate in the body.
- Assessment of potential carcinogenicity, in the context of genotoxicity, and any relevant non-genotoxic modes of action identified when characterising systemic toxicity.
- Characterisation of local effects (skin sensitisation potential, eye and skin irritation).
- Characterisation of systemic toxicity based on BER calculation.
- Analytical characterisation of the commercial specification of the material and expected contaminants.

Data/information available:

(In addition to the *in silico* predictions and *in vitro* screening assays generated during the Ingredient Discovery and Development Phases)

- *In vitro* genotoxicity data generated to showing lack of genotoxicity, hence genotoxic carcinogenicity is unlikely)

[12] Points of departure such as no observed adverse effect level (NOAEL) benchmark dose modelling to identify the lower confidence interval of a 10% increased incidence of tumours (BMDL10)

- In addition to *in vitro* peptide reactivity data generated suggesting the material is unlikely to adduct to protein, KeratinoSense™[13] and U-SENS™MUSST assays indicate a lack of nrf-2 and CD86 induction, key events in the skin sensitisation AOP. Hence, the biosurfactant is considered unlikely to cause skin allergy.
- Skin penetration conducted in a hand dishwash formulation relevant to the product to be marketed. As the biosurfactant was anticipated to poorly penetrate the skin, a radiolabel study was carried out to enable sensitive detection.
- Immune effects characterised, including complement activation, pyrogenicity (endotoxin like effects) and anti-rhamnose anti-body binding, demonstrating that immune effects are unlikely at consumer exposure levels.
- Critical micelle concentration (CMC) generated for the biosurfactant and benchmarked to the CMC of marketed surfactants. The CMC value confirmed relative mildness of the surfactant.
- To ensure adequate biological coverage of potential systemic effects the data outlined in the systemic safety toolbox described by Middleton et *al.* (2022)[14] are generated. These include high-throughput transcriptomics, a cell stress panel, and in vitro pharmacological profiling (PBK modelling was not included due to absence of exposure via the dermal route and limitations existing at present to model mixtures).

Key questions and considerations and major uncertainties:

- Will further scale up impact the specification of the raw material?
- Do the BERs calculated demonstrate sufficient margin of safety for the proposed use?

Conclusion: Due to negligible exposure via the dermal route the BER calculated based on the broad health range of health effects assessed shows low risk of systemic toxicity.

Occupational Safety:

Much more detailed process development and formulation design work would be conducted at this stage to understand manufacturing requirements for scale up and full-scale manufacture of the product. Process and occupational safety risks arising from other formulation changes that may be needed to enable the biosurfactant to be included in the product will also need to be assessed.

Illustration through the biosurfactant example:

Objective/Scope of Assessment: Assess process related risks for development activities and as design inputs to the subsequent full-scale manufacture of the consumer products. Application of inherent safety approaches and defining an appropriate basis of safety to manage residual risks throughout the whole process.

- *Risk Assessing Development Activities*

[13] Test No. 442D: In Vitro Skin Sensitisation - ARE-Nrf2 Luciferase Test Method (oecd-ilibrary.org)

[14] Middleton, A.M., et al 2022. Tox Sci, 189(1), pp.124-147.

Whilst a more complete chemical/biological characterisation for the biosurfactant should start to become available at this stage with a better understanding of the hazards, this information may not be totally complete and risk assessments for handling the material and the formulated cleaning product in the process development work will be needed.

Where data gaps exist, a precautionary approach for minimising worker exposures using strict risk management measures for handling the biosurfactant and the formulated cleaning product will be utilised to enable development and scale up activities to progress. Development activities would also need to consider other hazardous properties, such as potential flammability or combustibility risks depending on biosurfactant form, with appropriate levels of testing conducted to better quantify risks, as necessary.

- *Early-Stage Process Design Review (for full scale operation)*

In many instances, a structured hazard assessment for the proposed full-scale process design (including alternative options) would be conducted and this provides a good opportunity to assess the potential occupational safety of the biosurfactant.

Given that the biosurfactant would be incorporated into the cleaning product in an existing manufacturing facility (and therefore process), there will be detailed knowledge of the existing process and associated equipment. For this reason, the review would focus on the requirements for introducing the material into an existing manufacturing system, assessing implications between multiple factors and constraints (e.g. safety, costs, quality requirements etc.). Outcomes from the study could also influence the process development activities, including the nature of the biosurfactant itself (e.g. form, concentration etc.).

Data/information available:

- The specific format/concentration of the biosurfactant together with key physical/chemical properties should be known by now. These parameters will strongly influence the process design requirements for safe handling and inclusion of the material in the consumer product.
- A good understanding of the residual hazards associated with the biosurfactant and potential impacts on process design/worker exposure risks. For instance, characterisation of the biosurfactant had already indicated no significant allergy risks nor the presence of pathogenic bacteria.
- A well-developed/complete supplier safety data sheet for the biosurfactant.
- Proposed product formulations.
- Proposed process and formulation changes for incorporating the biosurfactant in the consumer product.
- Scale of operation (as input to most appropriate means for handling materials and their associated risks).
- A good understanding of the environmental hazards to assess implications of spills or wastewater treatment etc.

Key questions and considerations:

- Current constraints and process capabilities of the existing process for manufacture of the consumer product.
- Environmental safety data on factory waste streams and the ability to handle or treat these.
- Prior to moving to full implementation, Unilever and the biosurfactant supplier will also need to define a specification for the biosurfactant that meets the product safety and quality

requirements that the supplier can reliably achieve. This will need to be verified by the supplier as part of their process development and ongoing production activities to assure Unilever that the biosurfactant manufacturing process yields a consistent product which meets the agreed specification. For example: Is there batch-to-batch variability of the biosurfactant? Are sufficient controls in place to ensure the bacteria used for fermentation do not change? Are the quality requirements, contaminant levels and microbial specifications for the feedstock and other materials used in the process, together with the resultant biosurfactant product, understood and defined? Can a comprehensive safety data sheet be generated for the biosurfactant?

Conclusion: Sufficient toxicological information is now available to fully characterise worker safety risks and define suitable risk management measures. More detailed risk assessment activities aligned to the proposed dishwash liquid manufacturing process need to be completed to confirm all risks have been addressed and identify whether other data/information may be needed to complete the understanding of risks for scale up and full-scale manufacture.

Environmental Safety:

Much of the environmental safety work required to progress the lead candidate to development and testing will already have been conducted. When lead technologies are new to the Unilever portfolio, the market volumes used in the assessment are based on the intended use alone. Additional environmental safety assessments of the other ingredients to be used in the final formulated product would be conducted at this stage. Where these are already present in the Unilever portfolio the additional market volume of each ingredient in each market country is added to existing volumes and the assessment is done based on this new 'Total Tonnage'.

Based on these assessments, additional data generation may be necessary for any of the ingredients such as non-animal NAM based weight of evidence approaches or refinements to the exposure assessments to reduce conservatism and increase realism.

Illustration through the biosurfactant example:

Objective/Scope of Assessment: Environmental safety assessment of other ingredients in final product containing the biosurfactant based on marketing plans

- Necessary data generation and prospective safety assessment for all ingredients in the product taking a "Total Tonnage" approach.

Data/information available:

- Incremental volume adjustments for ingredients in the product that are already used within Unilever's portfolio and have been demonstrated to be safe.

Key questions and considerations:

- Ongoing partnership with R&D and marketing teams to ensure market volumes and countries used in prospective assessment for years 1 to 3 post launch are valid, noting that roll-out may occur in successive phases.

Conclusion: Prospective safety assessments in place for the biosurfactant and other ingredients within the new product demonstrate safety prior to launch.

Environmental Sustainability:

Quantitative life cycle assessment is possible given the availability of formulation information as well as value chain process flow information. LCAs may be streamlined to focus on impact categories anticipated as material for the technology in question. Assessment may be tiered from standard LCA screening through to high tier prospective and spatially resolved LCA.

LCA approaches employed during this phase are intended to help confirm environmental impacts and benefits of the biosurfactant selected as lead candidate relative to existing technologies in use (i.e. petrochemical and oleo surfactants) at product level. It can also help optimise processes (efficiency, sourcing locations, energy and material sources etc) and possibly consider scaling effects for different phases of intended application (e.g. considering the non-linearity of environmental impacts due to volume increases associated with different phases of intended roll-out).

Illustration through the biosurfactant example:

Objective/Scope of Assessment: Assess implications of technology use in products, based on critical factors identified above.

- Phase 1: Assess environmental impacts and benefits of the biosurfactant in a product context. Comparative assessment at product level – Dishwash formulation containing novel biosurfactant vs petrochemical and oleo surfactants (including surfactant reduction scenarios in cases where novel surfactant works well at lower levels of inclusion).
- Phase 2: Investigate potential for optimisation of the biosurfactant supply chain. Assess biosurfactant through a prospective, spatial modelling approach – land use change improved-life cycle assessment, or LUCI-LCA (Chaplin-Kramer et al., 2017[15]) – allowing for a detailed consideration of land use and land use change implications of feedstock sourcing: greenhouse gas emissions, biodiversity loss, soil erosion and nutrient pollution. Key objective to evaluate potential non-linear environmental impact responses to different demand scenarios for biobased feedstocks. Considers a.) feedstock supply from existing supply base, b.) intensification of existing agricultural land, and c.) expansion of agricultural land.

Data/information available:

- Product formulation data based on existing formulations: potential reduction in overall surfactant levels (no other reformulation considered).
- Production data provided by supplier: scenarios to represent full-scale production in three different geographies (based on engineering estimates of potential energy and material use).
- Information on feedstock types and potential sourcing locations
- Globally available, spatial data for regions from which feedstock will be sourced

Key questions and considerations:

- Phase 1: Product level assessment shows potential benefits of using biosurfactant in hand dishwash compared to traditional surfactants, but only when increased efficiency is considered: if

[15] Chaplin-Kramer, R. et al. 2017. Nat Commun 8, 15065.

lower surfactant levels can be achieved with biosurfactant, this leads to lower impacts of products. Further assessments are required to consider feedstock sourcing options (land use and land use change impacts) under different demand scenarios associated with scaling the technology.

- Phase 2: The assessment revealed that there is large variability in impacts from different feedstock sourcing scenarios. The assessment also found that although the total impacts from the sourcing of larger volumes are obviously higher, this is not necessarily the case when impacts are considered per kg of surfactant: GHG impacts can be lower at bigger scale when expanding agriculture in certain locations (i.e., non-linear scaling dues to higher carbon stock forest gets degraded first, followed by a lower carbon stock forest).

Conclusion: Phase 1 provides key insights into drivers of impact and highlights product formulation conditions for improved environmental outcomes (i.e., % surfactant reduction). Improved efficacy of surfactant means reduced amount included in formulation delivering environmental improvements over existing formulation. Potential GHG benefits identified as well as opportunity to stress test via assessment of possible land use / land use change and scale-up scenarios. In phase 2, a LUCI-LCA is applied to provide a prospective and spatially explicit examination of the variability and non-linearity of environmental impacts due to anticipated feedstock sourcing strategies (crop type and location) and demand forecasts for roll-out phases.

It is worth noting that in all phases, a selection of LCA indicators deemed most relevant when it comes to bio-based ingredients have been selected, meaning that not all possible LCA indicators are included. Additionally, as noted previously, the nature of the innovation being assessed will raise different questions with regards to its potential benefits, that are not necessarily captured by standard LCA approaches. In the case of bio-based surfactant feedstock expansion, LUCI-LCA was required to understand the non-linear effects of volume scaling. Undertaking a LUCI-LCA is not a common practice in the innovation process but was deemed especially relevant in the case of biosurfactant. However, it should be noted that LUCI-LCA is not applied as a default assessment approach for all innovations. Such assessment was applied only because land use change impacts were identified as a critical factor requiring further assessment to understand implications of scaling in the previous step.

Production and Launch

The production and launch phase is the culmination of all the innovation stages including the safety and sustainability evaluations through the product design. At this stage, based on the information generated throughout the whole development process, the necessary risk assessments to provide confidence that consumer, occupational and environmental safety risks have been satisfactorily addressed will be complete. Relevant LCA assessments will have also been conducted to establish environmental sustainability and to identify improvement opportunities across the anticipated value chain. There may still need to be some validation work to confirm some of the inputs to the risk and impact assessments (for example, validation that the levels of residual components in the biosurfactant remain within the risk assessment boundaries once full production is underway). There may also be a need to obtain further data to refine individuals' exposure estimates (consumers and/or workers). For example, if consumer or operator skin complaints were observed following introduction of the material, there would be follow-up investigations to determine potential causes. Ongoing partnership with R&D and marketing colleagues provides awareness of potential product or brand claims which may require refinement or extension of impact assessments (e.g. refining or extending LCAs if environmental claims are anticipated, depending on claim type and market).

Consumer Safety:

At this stage the consumer safety assessment of the biosurfactant in the formulation is finalised. Consideration is made for any interaction with other components of the product formulation e.g. additive effects with co-ingredient with the same toxicological mechanism of action as the novel biosurfactant or potential reactions between formulation ingredients.

A final check is made to ensure that the safety assessment carried out during the Development and Testing stage is relevant to the commercial specification and the consumer exposure scenario/s are still relevant once locked.

Illustration through the biosurfactant example:

Objective/Scope of Assessment: review of all exposure and hazard data collected and ensure applicability to finalised product formulation and commercial material specification. Safety assessment carried out based on the data above.

Data/information available:

(In addition to the data generated during previous phases; where necessary studies have been re-run on commercial specification)

- **Composition:** Confirmed specification of raw material for inclusion in formulation with robust data on purity, and contaminants of concern (e.g. protein and endotoxin).
- **Consumer Exposure:** Locked level (%) of raw material to be used in formulation enabling finalised deterministic exposure calculations for dermal exposure and residues on crockery resulting in transfer to food and hence oral exposure to the consumer.
- **Genotoxicity & Carcinogenicity:** *In vitro* genotoxicity data generated to showing lack of genotoxicity, hence genotoxic carcinogenicity is unlikely).
- **Skin Sensitisation:** weight of evidence from in vitro indicate the biosurfactant is unlikely to cause skin sensitisation.
- **Protein Allergy (Type I):** Levels of residual protein in the material pose are unlikely to trigger type I allergy.
- **Immune effects:** Sufficient margin of safety for immune effects, including complement activation, pyrogenicity (endotoxin like effects) and anti-rhamnose anti-body binding.
- **Local irritation:** Critical micelle concentration (CMC) generated for the biosurfactant and benchmarked to the CMC of marketed surfactants. The CMC value confirmed relative mildness of the surfactant; together with feedback from controlled consumer tests, suggest this local skin irritation is likely to be well tolerated.
- **Systemic Toxicity:** To ensure adequate biological coverage of potential systemic effect the data outlined in the non-animal NAM based systemic safety toolbox described by Middleton et *al.* (2022)[16] are generated. These include high-throughput transcriptomics, a cell stress panel, and in vitro pharmacological profiling. Bioactivity Exposure Ratios (BERs) were calculated with biological effect levels as points of departure, this was also context of the TTC and the calculated CMC in blood to provide additional confidence of a lack of adverse toxicological effect.

[16] Middleton, et al, 2022. *Tox Sci*, *189*(1), pp.124-147.

Key questions and considerations:

Conclusion: all relevant potential human health effects have been identified and addressed for consumer exposure to the biosurfacant in a hand dishwash formulation. The biosurfactant and its potential contaminants have been shown to be non-genotoxic and non-sensitising. The irritancy potential of the biosurfactant (both eye and skin) is relatively mild compared to other marketed surfactants. The BER calculated shows a large margin between potential systemic effects and realistic worst case consumer exposure.

Occupational Safety:

At the time the technology is ready to move to full scale production of the consumer product, all the hazardous properties for the biosurfactant should be fully defined (including any hazards posed by chemical or biological contaminants). In the development phase, the most significant hazards would have been considered when selecting the handling and processing methods with the aim of using inherent safety principles to avoid/minimise the highest risks, as far as possible, or by selecting control measures that limit worker exposures (respiratory, skin, oral etc.) This would include the handling requirements for the biosurfactant itself and for handling intermediate mixtures and the finished product throughout the manufacturing process.

To finalise the review of potential health risks to workers, a detailed review of the entire process should be carried out to confirm that all potential exposures throughout the process have been identified, with sufficient controls in place to provide an adequate margin of safety for each specific hazard. The final design review would not only need to consider exposures from the routine manufacturing steps but also include other related workplace activities, such as cleaning and disinfection, maintenance activities, dealing with spillages, handling rework etc. Other means of protection may be required for such activities that will subsequently need to be implemented and built into operator training and operating procedures.

A structured safety review of the final process design would also need to assess any other physical hazards posed by the biosurfactant (for example, if the material was flammable or combustible under the process conditions used) as well as potential environmental impacts such as the generation of wastes/waste streams or spill protection requirements.

Conclusion: All relevant worker safety risks associated with the biosurfactant and implementing it in the dishwash liquid process have been reviewed and addressed, with appropriate risk management measures in place to protect workers – both for routine manufacture and for specific, non-routine tasks (e.g. cleaning up spills).

Environmental Safety:

Following launch, the environmental safety of all ingredients is monitored through annual 'Total Tonnage' assessments for all Unilever uses in all market countries. These assessments provide assurance that Unilever use of ingredients can be demonstrated to be safe, and they are used to identify potential refinements to the conservative assessments where safety margins are narrowing. Ongoing interaction between the safety scientists and R&D colleagues developing new innovations and marketing plans on product launches also inform these assessments and the need for refinements. Options for these refinements are varied and specific to the ingredient being assessed and can include sourcing additional data on ingredient fate or effects, non-animal NAMs based effect

data generation, fate data generation, more refined exposure assessment such as more spatially derived approaches[17]. Ultimately, risk management through restrictions to Unilever use of a material are possible outcomes if safety margins are expected to be exceeded and investment in further refinement of assessments is no longer considered viable.

Illustration through the biosurfactant example:

Objective/Scope of Assessment: Ongoing monitoring of market volumes to ensure continued safety

- Annual assessment of safety based on updated market countries and volumes across all Unilever uses of the biosurfactant.

Data/information available:

- Prospective information on new launch plans and market volumes alongside retrospective information on volumes from previous year

Key questions and considerations:

- Can environmental safety of Unilever use of the biosurfactant continue to be demonstrated as market countries and volumes change?
- Are additional data required to refine the previous conservative assessments in order to assess safety based on new market information?

Conclusion: Ongoing monitoring of the safety assessment of Unilever use of the biosurfactant maintains confidence that additional uses remain safe for the environment. If safety margins based on previous conservative assessments reduce, additional data generation and refinements to the assessments can be done.

Environmental Sustainability:

Typically, the completion of a full LCA assessment would only be undertaken during this last phase to support a specific claim on the sustainability benefits of the product/material. Such assessment would be used for claim substantiation and would be tailored to the specific claim context / market(s).

Illustration through the biosurfactant example:

The evidence of lower environmental impacts, supporting biosurfactant inclusion in formulation was provided in the previous sections. In this instance, environmental sustainability claims were not intended, therefore no final LCA assessment was required.

If environmental sustainability claims had been pursued, post-launch support may be required to maintain such claims. For instance, if they were continued over several years then data updates may be required, or if the product was subsequently rolled-out to other markets, market specific assessment (reflecting differences in supply chains and therefore transport or grid mixes for manufacturing etc.) might be needed.

[17] Kilgallon et al 2017. Environmental Pollution 230 pp 954-962.

Closing Remark

The assessments outlined in Part 1 and this Annex illustrate the step-wise process undertaken through the various innovation phases. However, whilst safety and sustainability are assessed through product design, not all steps are always necessary for every innovation. For example, if screening environmental sustainability assessments undertaken in early innovation demonstrate significant benefits, then subsequent analysis may not be required unless environmental claims are anticipated. Conversely if gross negatives for safety or sustainability are identified early on, with no potential to mitigate these, then technology options / the entire project may be abandoned negating the need for further evaluation.