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Detergents

Detergent Chemistry Modulates the Transgression of Planetary Boundaries including Antimicrobial Resistance and Drug Discovery

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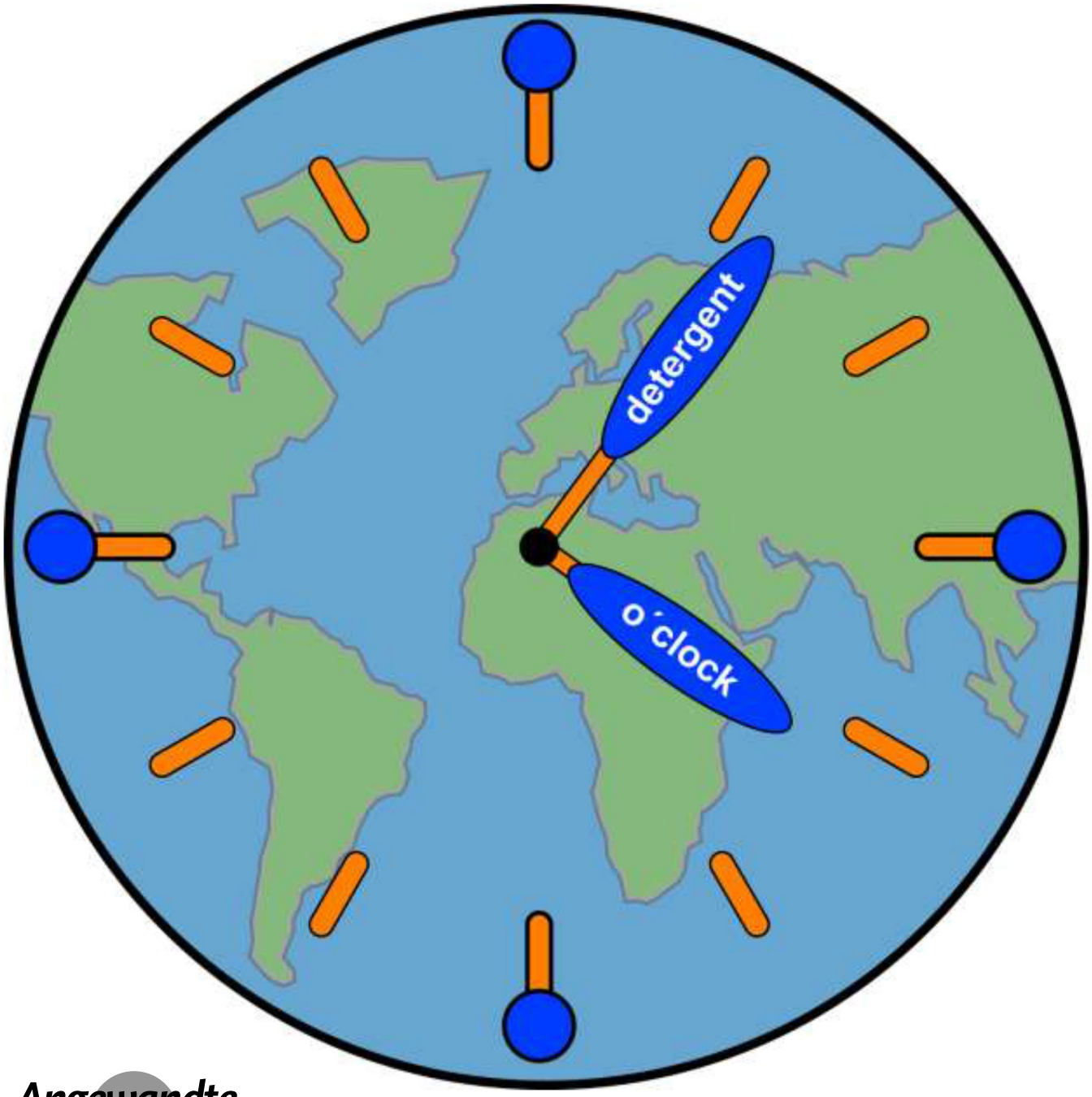

Abstract: Detergent chemistry enables applications in the world today while harming safe operating spaces that humanity needs for survival. Aim of this review is to support a holistic thought process in the design of detergent chemistry. We harness the planetary boundary concept as a framework for literature survey to identify progresses and knowledge gaps in context with detergent chemistry and five planetary boundaries that are currently transgressed, i.e., climate, freshwater, land system, novel entities, biosphere integrity. Our survey unveils the status of three critical challenges to be addressed in the years to come, including (i) the implementation of a holistically, climate-friendly detergent industry; (ii) the alignment of materialistic and social aspects in creating technical solutions by means of sustainable chemistry; (iii) the development of detergents that serve the purpose of applications but do not harm the biosphere in their role as novel entities. Specifically, medically relevant case reports revealed that even the most sophisticated detergent design cannot sufficiently accelerate drug discovery to outperform the antibiotic resistance development that detergents simultaneously promote as novel entities. Safe operating spaces that humanity needs for its survival may be secured by directing future efforts beyond sustainable chemistry, resource efficiency, and net zero emission targets.

1. Introduction

Earth's resources are limited and so is the ability for humanity to grow on planet Earth. The development of a paradigm that integrates the continued development of human societies and the maintenance of Earth system is supported through the planetary boundary framework.[1] The science-based analysis of the planetary boundary concept defines 'safe operating spaces' for humanity. Nine aspects of anthropogenic threats to critical Earth systems were identified, for each of which safe operating spaces were defined with respect to nine planetary boundaries and their threshold levels (Figure 1).[2] In many cases, control variables that were chosen as indicators for monitoring the transgression of planetary boundaries are chemical entities.[2] If these thresholds are crossed, the environment may lose the ability to self-regulate. Important subsystems, such as lakes or coral reefs, could shift into a new state with potentially serious consequences for humanity.[1a,3]

Six of the nine planetary boundaries are transgressed,[1b] suggesting a need for a deeper understanding and modification of underlying processes promoting this transgression (Figure 1). To secure safe operating spaces that humanity needs for its survival, chemists can contribute to restore stability and strengthen resilience of the planetary system.[2] Specifically, chemists can work on understanding the nature of the looming threats, harness innovations that are central to the practice of chemistry to develop sustainable solutions, and transform chemistry itself to a driver for sustainability and better stewardship of resources on planet Earth.[2]

With climate change being obviously associated with chemistry, much effort has been spent on monitoring and reducing carbon dioxide emissions.[4] Another chemically relevant boundary that raises global interest is novel entities (Figure 1). Novel entities are chemicals that are novel in a geological sense and could have large-scale impacts on biodiversity.[5] Detergents are amphiphilic molecules that can make substances with opposing polarities miscible which enables a diverse range of applications, such as laundry, cleaning, or emulsifying.[6] However, due to their amphiphilic properties, detergents also interact with cell membranes during applications or along disposal routes, sometimes with harmful consequences for the biosphere, such as antimicrobial resistance development.[7] To minimize the role of novel entities on the transgression of planetary boundaries, holistic design approaches are needed that optimize the full life cycle of detergents, including production, application, and disposal.

Recent reports on consequences for the biosphere imply an unmet need for a holistic design thinking beyond the known necessities for the prevention of climate change. Previous reviews on detergent chemistry focus on niche topics, like protein purification, antimicrobial resistance, or antiseptics, and do not cover the holistic impact that detergent chemistry currently has on planet Earth. However, an overview on the current state of detergent chemistry in context with Earth's resources is pivotal to guide future efforts that minimize the transgression of planetary boundaries. Herein, we close this gap by establishing a method for literature search that allows us to analyze the impact of detergent chemistry on Earth's resources more holistically (Figure 1). First, we analyzed obvious paradigms that are associated with detergent life cycles and affect the transgression of planetary boundaries (Figure 1). This led us to five boundaries that are most obviously affected by detergent chemistry, including climate, land system, water, freshwater change, novel entities, and biosphere integrity. Second, we assessed current literature knowledge on the impact that detergent life cycles can have on our five designated planetary boundaries (Figure 1). Third, we obtained a more holistic overview of the state of detergent chemistry in context with Earth resources, including boundary-specific challenges and underappreciated cross-boundary interactions.

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2. Results and Discussion

2.1. Climate, Land System, and Freshwater Change

In the first part of this review, we analyzed interactions between detergent chemistry and planetary boundaries with relevance to a holistically, climate-friendly detergent industry. Climate change is advancing globally, and the consequences are becoming increasingly noticeable. Major contributions to the transgression of climate change come from industrial detergent production and packaging. While the majority of detergents is still of petrochemical origin,[8] detergent industry undergoes a paradigm shift towards renewable sources to reduce carbon dioxide emission.[9] Bio-based detergents are wholly or partly derived from materials of biological origin and expected to drive future market growth.[9–10] Substituting plastic packing material for cardboard packaging and recycling of packing material are strategies to reduce carbon dioxide emissions.[11] However, minimizing the transgression of a planetary boundary selectively is difficult due to the entangled nature of Earth's sub-systems.[1] For example, substitution of petrochemicals for bio-based production cycles may reduce carbon dioxide emissions but at the same time it can promote the transgression of land system and fresh water change. Bio-based detergents obtained from plant resources, i.e., palm oil, require farmland and freshwater. Expanding farmland to increase bio-detergent production promotes regional changes in climate, water scarcity, diversification, and biodiversity (Figure 1).[12] Bio-based detergents, such as rhamnolipids,[13] can be a more climate-friendly substitute for petrochemicals, provided that the methods for obtaining and producing them are ecologically sustainable.[8b] Biomass waste that would be trashed otherwise seems to be a valuable resource for detergent production.[14]

Green chemistry practices in detergent industry and academic teaching have been reviewed in detail.[5f,15] This brings us to the status of the second challenge that is the alignment of materialistic and social aspects in creating technical solutions by means of sustainable chemistry. The role of lab routines in academic laboratories dealing with detergent chemistry remains underappreciated. Another literature survey analyzed 265 publications to picture recent trends in detergent chemistry, 121 of which reported

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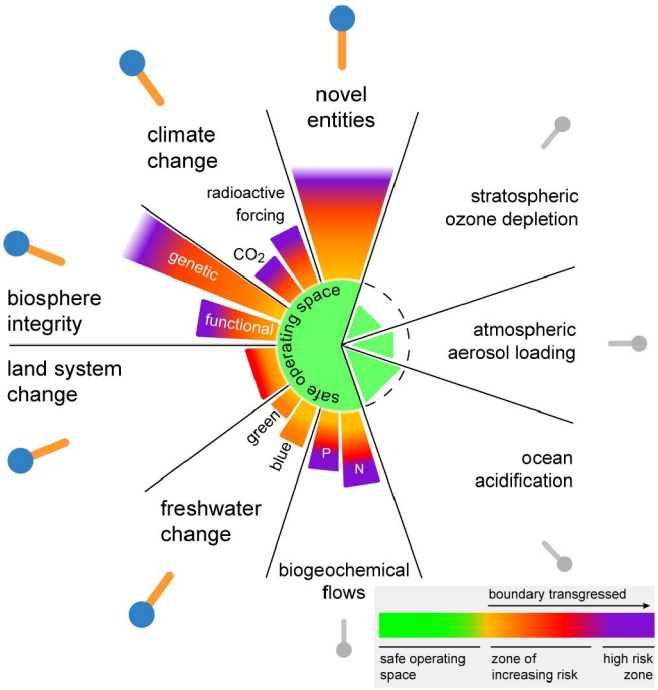

Figure 1. Detergents modulate the transgression of planetary boundaries. Herein, the impact of detergent chemistry is reviewed for five of the six planetary boundaries that are currently transgressed. Image was adapted from an original image shown in reference[1b] with minor modifications (CC BY-NC 4.0).

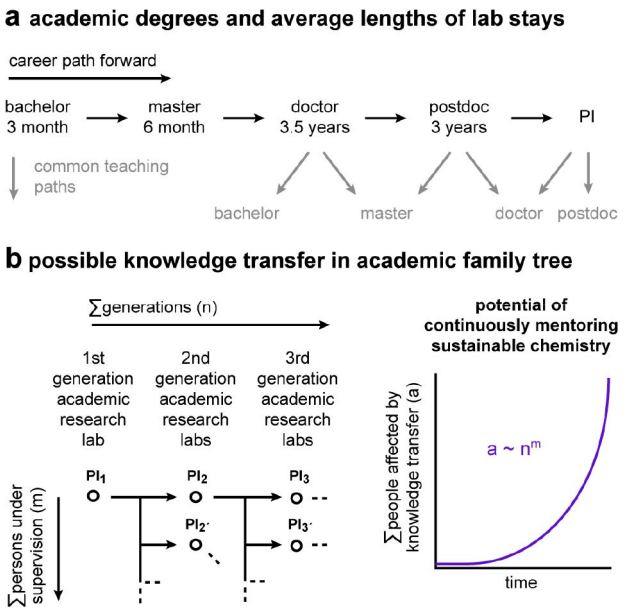

Figure 2. Social relevance of academic detergent chemistry for climate. a Overview of career steps in chemistry and average lengths of lab stays. Knowledge on lab routines acquired at any career stage can be passed on when a person transfers it to pupils at other career stages. b Overview of leverage in knowledge transfer from a parent academic research lab (1st generation) to the next generations of academic research labs. The diagram visualizes the number of people affected by knowledge transfer over time, from the perspective of academic family trees.

detergent synthesis by means of petrochemicals.[9] Compared to industry, the immediate impact of academic lab routines from a single project on the transgression of planetary boundaries may be neglectable. However, academic lab routines are commonly passed onward from teacher to student without third party regulation.[16] This includes consolidated, climate-harming lab routines, like the use of petrochemicals for reactions and purifications. The time spent by a person in academic research labs depends on the actual degree, varies from months to years, and is usually longer than the duration of lab teaching courses (Figure 2a). However, a student may become a supervisor and will transfer acquired knowledge to the next generation of scientists (Figure 2a). The rise in number of people (n) confronted with this knowledge transfer over time can be approximated by an exponential model (Figure 2b).

Even though our approximation may not reflect true reality, it exemplifies the potential that continuously mentoring sustainable lab routines can have on modulating the transgression of climate change, from a social perspective. In addition, research projects are commonly urged to justify materialistic resources in proposals to meet societal demands.[17] Scientific award Schemes can help to strengthen visibility of sustainable innovations, stimulate knowledge transfer and encourage scientists to adopt climate-friendly lab routines. Aligning both materialistic and social aspects in creating technical solutions by means of sustainable chemistry will leverage the impact that funding decisions can have on the transgression of planetary boundaries, including climate change.[2]

2.2. Biosphere Integrity and Novel Entities

2.2.1. Medical Detergents Secure Human Integrity in Earth's Biosphere

Having analyzed the most obvious impact of detergent chemistry on climate change, we now shift our focus to the third challenge, which is the development of detergents that serve the purpose of applications but do not harm the biosphere in their role as novel entities. The biosphere covers all living organisms and ecosystems. Maintaining its integrity is vital for functional feedbacks in the Earth system.[1b] To foster holistic detergent design approaches that minimize the transgression of biosphere integrity and co-affected boundaries, we reviewed the impact of medically intended and daily detergent uptake routes on human health (Figure 3).

Be it for hand washing, drug delivery, or the search of new pharmaceutical reagents, detergents are made to improve human health (Figure 3). At times of global aging and expanding populations, better medicines are desperately needed. Drug discovery is lengthy and costly. Owing to high failure rates of the current drug development process, biomedical research undergoes a paradigm shift towards

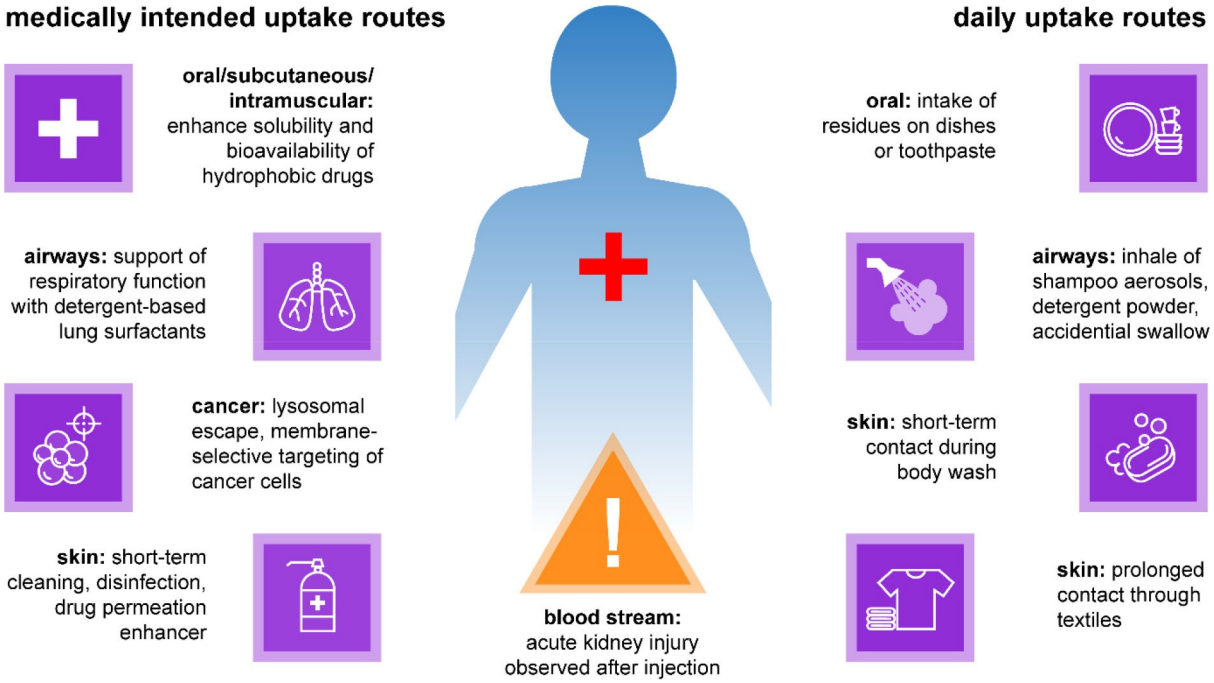

Figure 3. Detergents affect human health and integrity in the Earth system. Schematic overview of medically intended and daily detergent uptake routes. In both cases, oral, parenteral, and topical human-detergent interactions are widespread. Injections into the blood stream are rare and associated with kidney injury.

human disease models with the ultimate goals to improve clinical translations.[18] Complementary, detergent chemistry aims to tackle innovation hurdles in drug development, including drug solubility,[19] drug aggregation,[20] lysosomal escape,[21] proteomics-based drug target identification,[22] and structure-based drug discovery on membrane proteins.[23]

Technologies that promote drug solubility are crucially needed. Poor water solubility causes poor bioavailability – a speed breaker in drug discovery.[24] Oral drugs may not sufficiently absorb into blood circulation and can be excreted before reaching the side of action. Detergent aggregates can improve drug solubility and bioavailability. Detergent aggregates in water consist of a polar outer shell filled with detergent head groups and a non-polar inner core filled with detergent tail groups. The amphiphilic property of detergents enables the solubilization of hydrophobic drugs by aggregates (Figure 4a). Drug solubilization is optimized empirically and depends on the structures of detergents and drugs.[25] Furthermore, detergent aggregates are dynamic equilibrium with monomers and properties change with concentration. Co-localization of aggregates and encapsulated drugs cannot be guaranteed, which can limit utility for in vivo drug delivery.[9,26] Moreover, biocompatibility depends on the route of administration. Oral, subcutaneous, and topical applications with detergent formulations are common owing to higher biocompatibility to relevant tissue environments.[27] However, detergents may not be injected into blood streams. Treatable kidney injury has been diagnosed in rare cases where larger volumes of detergent formulations were injected into the blood stream, e.g., 20 mL and 40 mL.[28] Subcutaneous and intramuscular injections containing detergents are clinically relevant, like AquaMephyton® and Konakion® (Figure 4b).[27] Both examples underline that the solubilization power of detergent-drug formulations is often adjusted by mixtures of anionic and non-ionic amphiphiles – a principle that is also harnessed in transdermal drug delivery and laundry applications.[29] Cationic detergents must never be used in parenteral applications as they have their own pharmacological activity and antibacterial properties, which we discuss separately in context with detergent-microbial interactions.[27] Taken together, the utility of detergents as solubility promoters in drug discovery is well established, translated into clinics, and supports the integrity of humans in Earth's biosphere (Figure 3) (Figure 4).

Detergent chemistry also supports human health in preclinical, academic research by tackling drug aggregation,[20] and lysosomal escape (Figure 4b).[21] At micromolar concentrations, drug molecules can aggregate and non-specifically interact with proteins and membranes, which is linked to off-target effects. Comparing protein activities in response to ligands in the presence and absence of detergents can be used to identify aggregation-based mechanisms of action.[20] Ligands with aggregation-based mode of action can be removed early from drug discovery programs to improve clinical translation rates.

Bio-based detergents can modulate mammalian cell viability, which led to the idea to use detergents as cancer therapeutics.[5f] Intracellular transport pathways include drug binding to membrane surfaces followed by internalization into endocytic vesicles and the lysosome (Figure 4b).[21] Drug formulations may be ineffective if they cannot escape

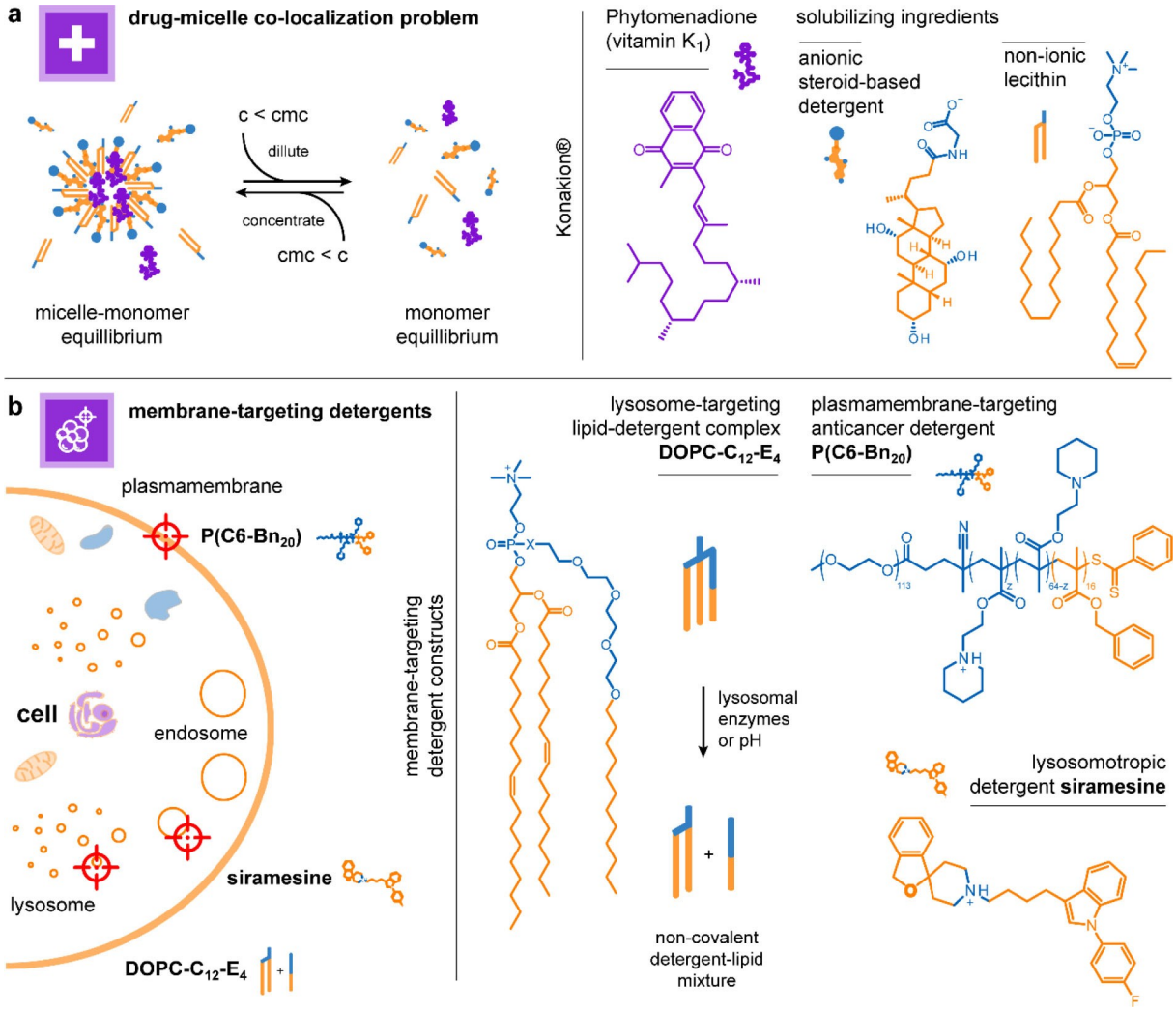

Figure 4. Opportunities and limitations of medical detergents in drug discovery. a Schematic visualizing the co-localization problem of drugs and detergent micelles. Clinically relevant Konakion® harnesses anionic, steroid-based detergent and lipids to solubilize water-insoluble vitamin K_1. b Schematic showing profile of a mammalian cell and membranes to be solubilized by different medically relevant detergent architectures.

the lysosome. Detergents can diminish the integrity of lysosomal membranes and facilitate lysosomal escape. Siramesine was identified as lysosomotropic detergent that can trigger cell death by destabilizing lysosomes, which opens new directions for combination therapies (Figure 4b).[30]

Combination therapies ideally co-localize lysosome destabilizing drugs and anticancer drugs in sufficient dose, which often cannot be guaranteed in vivo.[9,26] A promising direction are nanodrug vehicles that release covalently-bound detergent molecules upon cleavage. Pierrat et al. designed lipid-detergent conjugates for gene delivery (Figure 4b). Biodegradation of lipid-detergent conjugates inside the acidic endosomal compartment or upon exposure to lysosomal enzymes releases detergent molecules, which can destabilize membranes and facilitate the release of genetic material (Figure 4b).[31] In addition to detergents that target endosomal and lysosomal membranes, a nanodetergent was developed that can convert subtle pH perturbation signals into sharp changes in membranolytic activity, thus leading to selective plasma membrane rupture in more acidic tumor microenvironments (Figure 4b).[32] Harnessing the solubilizing and membranolytic properties of detergents enables new avenues for challenging drug delivery applications.

In addition to pharmacokinetic innovation hurdles, detergents enable the search for new pharmaceutical ingredients. Membrane proteins are targets for approximately 60 % of current drugs.[33] Detergents enable structure-based drug discovery of membrane proteins. Anionic detergents, like sodium dodecyl sulphate, are key enabling steps for proteomics applications that enable the search for biomarkers, assist with drug selection in personalized disease cases, and enable the identification of drug targets among signaling cascades.[22b] Non-ionic detergents with saccharide head groups, like *n*-dodecyl-β-D-maltoside and lauryl maltoside neopentyl glycol, are key enabling steps for the structural investigation of intact membrane protein complexes by condensed-phase techniques, like crystallography and cryo-electron microscopy.[34] Complementary, oligogly-

cerol detergents are the emerging enabling step for the structural investigation of intact membrane protein-ligand complexes by gas-phase techniques, like native mass spectrometry.[35] Detergents facilitate the search for new pharmaceutical ingredients and the investigation of membrane-ligand interactions with in vitro membrane models (Figure 5a).[36] To capture a recent overview on the chemical diversity of the detergentome, from the perspective of membrane protein research, we refer to other reviews.[9,22b,23b,36a]

2.2.2. Detergents are Novel Entities that Interact with Biosphere

Detergents are novel entities that can lead to severe consequences, not only for human health but also for the wider biosphere. Approximately 16 million tons of detergents are produced every year and around 60 % of it end up in aquatic ecosystems.[5c,f] Detergent pollution begins primarily in detergent-consuming hospital-, urban-, and industrial infrastructures via disposal into the sewers and can spread (Figure 5a).[5d,37] Detergent removal from wastewater is challenging. Wastewater treatment plants cannot quantitatively remove contaminants.[37c,38] Furthermore, micropollutant concentrations in hospital wastewater can be 80 times higher compared to domestic wastewater.[39] Hospital wastewater that is co-treated with domestic wastewater in conventional treatment plants contributes to the environmental co-pollution with detergents and pharmaceuticals.[5e] Detergents have been detected as emerging pollutants at different places in the world with implications for the wider biosphere.[40] Consequences for aquatic ecosystems include eutrophication,[40c] oxygen depletion,[5c] antimicrobial resistance development,[7] and changes in tissue structure in fish.[41] The fade of detergents in the environment can be accelerated by implementing cleavable groups.[42] However, treatment-resistant detergent degradation products are another emerging class of compounds whose biological activity remains to be explored.[40a] Interactions between detergents and all forms of life within the biosphere of planet Earth are more the rule than an exception.

2.2.3. Detergent Pollution Directs Bacterial Evolution and Antimicrobial Resistance

The detergent market is anticipated to increase and with it the input of detergents into the environment.[5f,43] A form of life whose interaction with detergents becomes increasingly relevant are bacteria. Quaternary ammonium-based detergents, like benzalkonium chloride (BAC) or alkyl ammonium bromides, are the most clinically relevant detergent class under debate as emerging pollutants and promoters for antimicrobial resistance development.[7b] The production, disposal, and environmental entry of BAC peaked in response to the COVID-19 pandemic as a consequence of ramped hygiene measures.[7b] Problematically, environmental co-pollution by detergents and antibiotics correlates with increased antibacterial resistance development along disposal routes (Figure 5b).[5e,44] Unsafe water consumption due to interactions between microbes

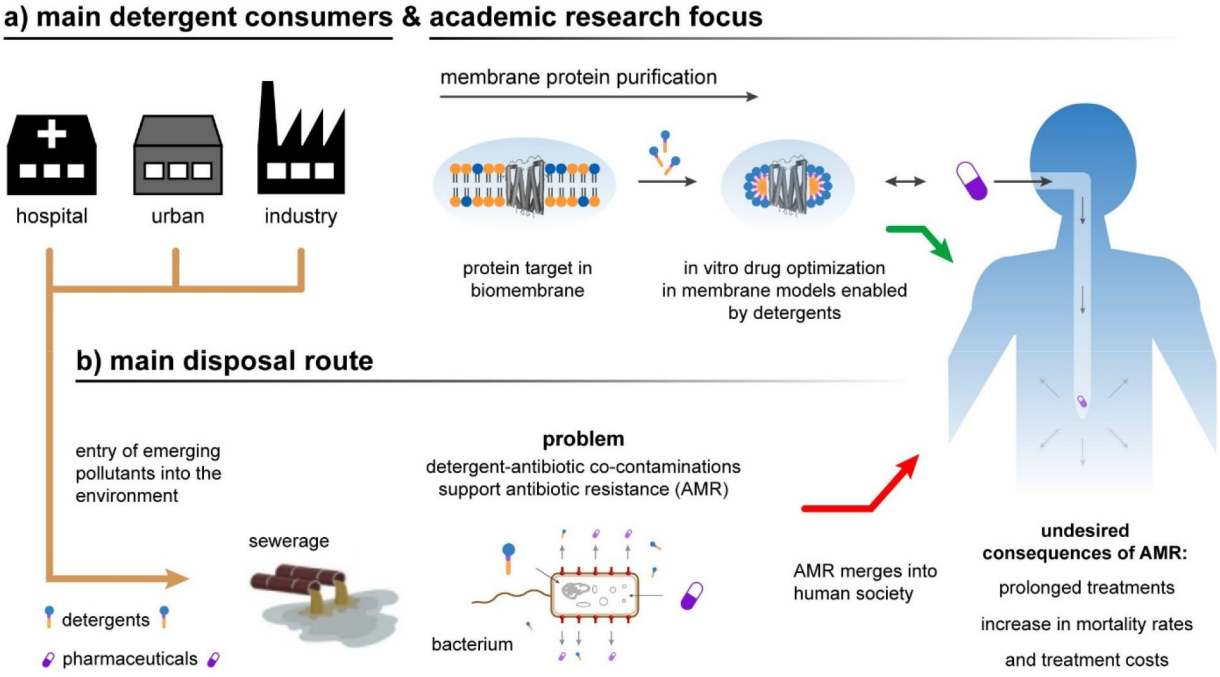

Figure 5. Detergents enable drug discovery and promote antimicrobial resistance. a Overview of main detergent-consuming infrastructures and a schematic highlighting the academic research focus on tailoring detergents to enable drug optimization on protein targets with in vitro membrane models. b Schematic showing the role of detergents as emerging pollutants in supporting antimicrobial resistance development.

and pollutions contribute to the emergence and spread of antimicrobial resistance, suggesting a need for a deeper understanding of underlying processes (Figure 5b).[5e]

At the genetic level, quaternary ammonium-based detergents can trigger the expression of resistance factors, like efflux pumps, that can increase the intrinsic bacterial resistance to antibiotics.[45,46] Detergents can facilitate the exchange of mobile genetic elements, thus supporting the exchange of resistance factors through horizontal gene transfer.[47] Alternatively, quaternary ammonium-based detergents can promote antimicrobial resistance development and spread by causing membrane perturbation, imbalance of osmosis, enzyme inhibition, dissipation of proton motive forces, and oxidative stress, all of which can induce mutations as consequence of error prone DNA replications.[48,5b] Moreover, quaternary ammonium-based detergents can also directly diminish the growth-reducing properties of antibiotics on bacteria.[49] Importantly, quaternary ammonium-based detergents may not automatically select for species with antibiotic-specific resistance genes. However, selection pressure can change antibiotic resistance profiles in bacterial communities in both directions, i.e., by selecting species that are either more susceptible or more resistant towards individual antibiotics.[7a] Shifts in microbiome profiles induced by detergents are not only relevant in clinical settings but also for modulating the smell of laundry[50] and the biological integrity of aquatic ecosystems, including wastewater and drinking water resources.[7a]

Are detergent-induced shifts in microbiome profiles relevant for antibiotic resistance in clinical settings? Literature analysis by J. M. Boyce consolidated the observation that multiple episodes of contaminated in-use disinfectants and antiseptics, which are often due to inappropriate use of products, have caused outbreaks of healthcare-associated infections.[51] The impact of quaternary ammonium-based detergents on bacteria and its clinical relevance are well documented.[5b,e,51–52] In contrast, less is known about the impact of non-ionic and anionic detergents which are also emerging pollutants.[5c]

Conversely, while detergent pollution contributes to the development of antimicrobial resistance, the optimization of detergents is increasingly communicated as key enabling step in membrane protein-based drug discovery (Figure 5b).[22b,23,36a,53] However, even the best detergent for membrane protein-based drug discovery cannot reduce the time required for transitioning from an original drug discovery idea to market entry. Drug development can take 10–15 years and is slower than the development of antibiotic resistances, which can become widespread within 2–3 years.[54] The number of FDA approvals for antibiotics has been declining for decades.[55] The number of deaths related to antimicrobial resistance likely increases until 2050, which can lead to a situation that is reminiscent to the era before antibiotics.[56] We conclude that the chemistry of detergents that secures human health without promoting antimicrobial resistance becomes increasingly relevant and needs to be explored.

2.2.4. Implications of Detergent Consumption for Human Health

Detergent science affects human health indirectly by supporting drug discovery and antimicrobial resistance development. However, detergents are also used to secure disease prevention and well-being by enabling personal hygiene, surface cleaning, and laundry. Owing to the chemical properties of detergents and circumstances of applications, human bodies get frequently into contact with detergents (Figure 3). Daily uptake routes include oral uptake, e.g., through detergent residues on dishes or the use of detergent-containing toothpaste;[57] inhalation, e.g., through shampoo aerosols or handling detergent powder;[5c,58] and skin contact, e.g., during personal hygiene measures and laundry (Figure 3).[59] Medically relevant case reports reviewed here outline concerns for human health, regardless of the uptake route.

To understand if detergents are generally harmful, we searched for publications that underline how detergents enable life. The airways of many terrestrial species are equipped with an approximately 0.1 μm thin film of pulmonary surfactants that lines the alveoli, reduces surface tension, and enables respiration.[60] C. Horwitz described lung surfactants as natural detergents probably due to similar surface tension-reducing properties.[61] However, lung surfactants are mixtures of lipids and proteins, whose molecular structures have not much in common with detergents (Figure 6). Owing to their membranolytic property, we expect detergents can destabilize fluid membrane structures formed by pulmonary surfactants that are required for the sufficient lining of alveoli and protection of underlying tissues. Detergent uptake into airways can induce development of allergies, inflammations, and pulmonary edema.[58,62] Membranolytic properties of detergents are a main cause for side effects, regardless of the uptake route, i.e., oral, airways, skin. For example, laundry detergents have proven epithelial barrier-opening effects in lung tissue and can induce eosinophilic airway inflammation by increasing IL-33 expression and activation of ILC2 s.[62b] In the case of detergent-containing dish washer formulations and toothpaste, epithelial barrier-opening effects were also observed in gut and mucosal tissue models.[57]

Safe-to-use detergents for everyday life routines are crucially needed. The problem with defining the chemistry of safe-to-use detergents comes with the wording. The term "detergent" can be used to describe a class of amphiphilic molecules or product formulations containing various amphiphilic molecules and additives. Some reports investigated biological effects in response to individual detergents[57a,59] and some focus on detergent-containing product formulations, often with complex chemical compositions.[57–58,62b] In the case of formulations, the impact of individual detergent molecules on experimental outcomes is difficult to delineate. Complementary, a clinical trial with an aerosol (Alevair) containing the detergent Triton WR1339 did not harm patients with chronic bronchitis but also did not produce benefits, suggesting that individual detergents may not be harmful for airways per se (Figure 6b).[63] The use of

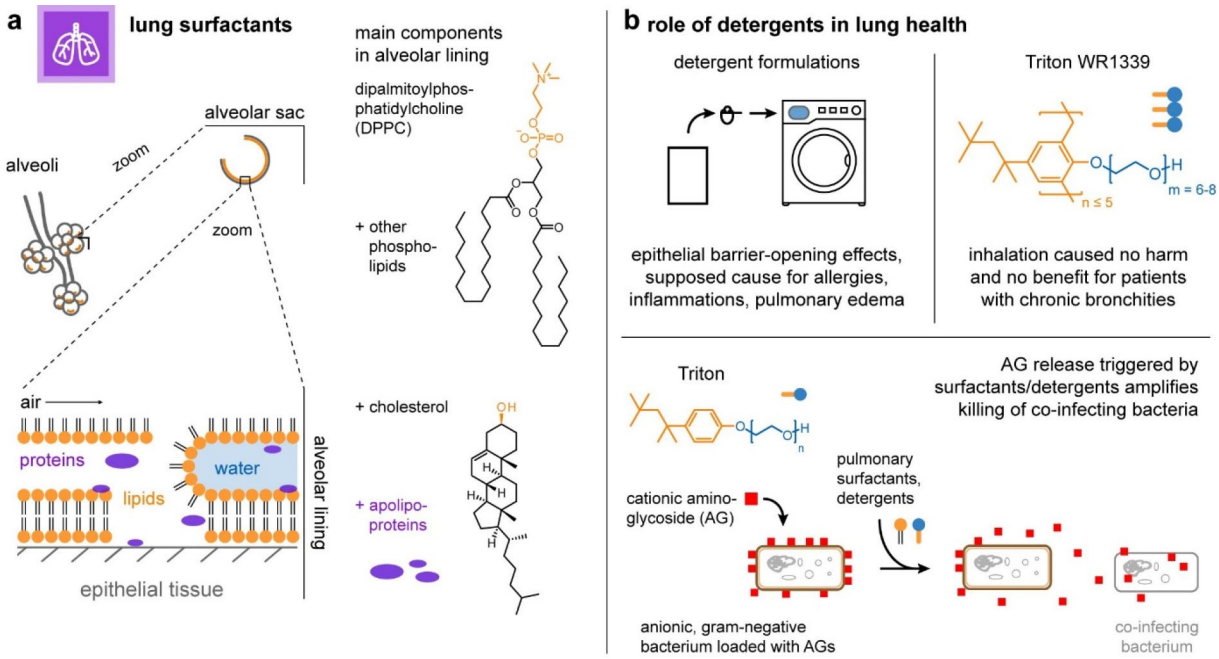

Figure 6. Detergents have opposing utilities for lung health. a Schematic showing the structure of alveoli, including the alveolar sac, alveolar lining, and main chemical components. b Schematic summarizing the role of detergents in lung health. Detergent formulations can negatively affect lung health, while individual detergent molecules may not always be harmful. Gram-negative bacteria can act as reservoir for aminoglycoside antibiotics whose release can be triggered by detergents and amplify the killing of co-infecting bacteria.[67] Downsides and benefits that can arise from the inhalation of detergents are mainly related to their membranolytic properties.

detergents is deeply integrated into our society. We expect future studies are required to delineate the role of detergent molecules from detergent formulations in human health, from a chemical biology perspective.

2.2.5. Membranolytic Properties are Curse and Blessing

Membranolytic property is a key parameter to define the impact of detergents on biosphere integrity. The term membranolytic property is used to describe the detergent's ability to interfere with structural integrity of cell membranes by inducing membrane dissolution. Cell membranes are held together by attractive hydrophilic and hydrophobic interactions between amphiphilic proteins and lipids. Following the motto *similia similibus solvuntur* (similar substances will dissolve similar substances), detergents can insert into membranes which affects structural integrity in a concentration-dependent manner. Detergent-induced membranolysis has been visualized through a three-stage model by Kragh-Hansen and co-workers (Figure 7a).[64] At low concentration, detergents insert into the lipid bilayer and are randomly distributed. At intermediate concentration, the lipid bilayer gets saturated with detergent molecules which interact cooperatively and induce a phase transition by membrane fragmentation. At high concentration, the phase transition reaches an end point at which proteins and lipids are solubilized in mixed micelles (Figure 7a). The uptake of detergent monomers into membranes is a key step for membranolytic activity.[65] However, above the critical micelle concentration, detergents are present as monomer-micelle equilibrium. Delineating the role of detergent monomers from micelles in biological feedback is a task for years to come.

Regardless of the mechanism, membranolysis causes stress that leads either to cell death or cell modulation, including genetic and functional feedback (Figure 7a). Driving forces for lipid membrane integrity include electrostatic and hydrophobic interactions between amphiphilic proteins and lipids. Since these driving forces are conserved across all species and also mediate interactions to amphiphilic detergents, membranolytic properties have been observed for all detergent classes, i.e., anionic, cationic, non-ionic (Figure 7b–d).[22] Herein, we complement this overview by summarizing recent findings on genetic and functional feedbacks. Specifically, cationic detergents, like BAC, are drivers for antimicrobial resistance.[66] It is unclear whether this is an intrinsic property of cationic detergents or specific for certain cationic detergent structures. Furthermore, it is unclear whether other anionic and non-ionic detergents, like SDS, alkyl benzenesulfonate (ABS), C12-C15 alcohol ethoxylates, behave differently compared to cationic detergents in terms of antimicrobial resistance modulation (Figure 7b–d). Moreover, the link between chronic detergent exposure, membranolytic properties, and inflammation has been established.[62b] While chronic cell stress can promote cancer development,[67] the contribution of sub-lethal detergent exposure to cancer development remains to be explored.

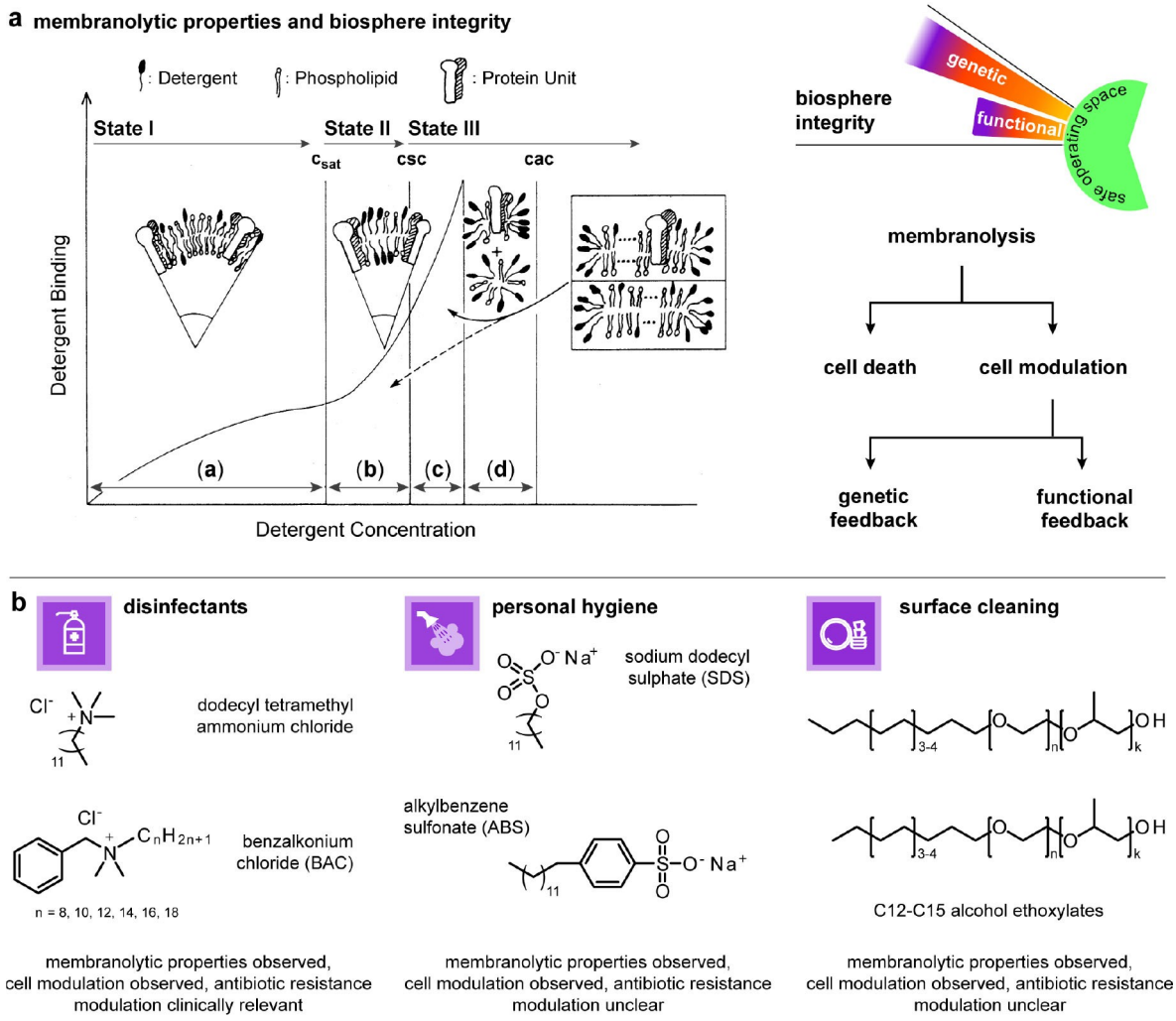

Figure 7. Membranolytic properties are curse and blessing. a Schematic of a three-stage model visualizing membranolysis at different detergent concentrations and related impact on biosphere integrity. b Common detergents in representative application fields and information on known consequences for biosphere integrity. The schematic of the three-stage model was adapted with permission from reference.[64] Copyright (2024) American Chemical Society.

3. Conclusion

In summary, we provided the most holistic description of the state of detergent chemistry in modulating Earth resources available to date. Specifically, we harnessed the planetary boundary concept as a framework to analyze the role of detergent chemistry in three critical challenges to be addressed in the years to come. Regarding the first challenge, which is to establish a climate-friendly detergent industry, our analysis underlines that bio-based detergents can be a true climate-friendly alternative provided that resources and methods for production are ecologically sustainable. Regarding the second challenge, which is to align materialistic and social aspects in creating technical solutions by means of sustainable chemistry, our analysis concludes the ability to instrumentalize knowledge transfer in academic families as an opportunity. Knowledge transfer in academic family trees can scale exponentially, which underlines the impact that continuously mentoring sustainable lab routines can have on modulating the transgression of climate change, from a social perspective.

Regarding the third challenge, which is the development of detergents that serve the purpose of applications but do not harm the biosphere in their role as novel entities, our analysis uncovered an ambivalent view on the detergents' utility for human health and wider biosphere. The irony is that detergent chemistry is practiced to secure well-being and human health while it causes harm in biospheres. From a global perspective, root causes to undesired consequences are cross-boundary interactions between novel entities and biosphere because of increasing detergent production and disposal volume. From a chemistry perspective, undesired consequences in biospheres are linked to the detergents' membranolytic properties. Membrane damage induces cell stress which leads to functional and genetic feedback in Earth's biosphere, including inflammation, antimicrobial resistance development, and maybe also cancer development. The overarching pattern in chemical composition of

detergents responsible for membranolytic properties is the amphiphilic character. The chemical design of polar and non-polar building blocks in detergents that serves the purpose of applications but do not affect cell membranes in biospheres is not well understood and needs to be explored, from chemistry and chemical biology perspectives. Herein, the challenge in knowledge transfer comes also with the wording. Putting more emphasis on clarifying whether detergent molecules or formulations are investigated in structure–activity studies will help to delineate the impact on biosphere integrity. We expect including the lessons learned from the description of the state of detergent chemistry in modulating Earth resources will foster new directions in developing detergents whose life cycles can minimize the transgression of planetary boundaries. We anticipate that utilizing the planetary boundary framework for literature surveys delivers a strategy to identify future research directions that can help to minimize the transgression of planetary boundaries, regardless of the chemistry.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data are available from the authors upon request.

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[1] a) J. Rockström, W. Steffen, K. Noone, A. Persson, F. S. Chapin III, E. F. Lambin, T. M. Lenton, M. Scheffer, C. Folke, H. J. Schellnhuber, B. Nykvist, C. A. de Wit, T. Hughes, S. van der Leeuw, H. Rodhe, P. K. Snyder, R. Costanza, U. Svedin, M. Falkenmark, L. Karlberg, R. W. Corell, V. J. Fabry, B. Walker, D. Liverman, K. Richardson, P. Crutzen, J. A. Foley, *Nature.* **2009**, *461*, 472–475; b) K. Richardson, W. Steffen, W. Lucht, J. Bendtsen, S. E. Cornell, J. F. Donges, M. Drüke, I. Fetzer, G. Bala, W. von Bloh, G. Feulner, S. Fiedler, D. Gerten, T. Gleeson, M. Hofmann, W. Huiskamp, M. Kummu, C. Mohan, D. Nogués-Bravo, S. Petri, V. Virkki, L. Wang-Erlandsson, L. Weber, J. Rockström, *Sci. Adv.* **2023**, *9*, eadh2458.

[2] S. A. Matlin, S. E. Cornell, A. Krief, H. Hopf, G. Mehta, *Chem. Sci.* **2022**, *13*, 11710–11720.

[3] M. Scheffer, S. Carpenter, J. A. Foley, C. Folke, B. Walker, *Nature.* **2001**, *413*, 591–596.

[4] a) Z. Liu, Z. Deng, S. J. Davis, C. Giron, P. Ciais, *Nat. Rev. Earth Environ.* **2022**, *3*, 217–219; b) R. B. Jackson, M. W. Jones, A. J. P. Smith, S. Abernethy, R. M. Andrew, A. J. De-Gol, D. R. Willis, Y. Shan, J. G. Canadell, P. Friedlingstein, F. Creutzig, G. P. Peters, *Nat. Clim. Chang.* **2020**, *10*, 647–653.

[5] a) L. Persson, B. M. C. Almroth, C. D. Collins, S. Cornell, C. A. de Wit, M. L. Diamond, P. Fantke, M. Hessellöv, M. MacLeod, M. W. Rydberg, P. S. Jørgensen, P. S. Jørgensen, S. U. Stockholm Resilience Centre, 106 91 Stockholm, Sweden, R. S. A. O. S. Global Economic Dynamics and the Biosphere, Lilla Frescativägen 4 A, 104 05 Stockholm, Sweden, P. S. Jørgensen, P. Villarrubia-Gómez, Z. Wang, M. Z. Hauschild, *Environ. Sci. Technol.* **2022**, *2022*, 1510–1521; b) S. Mohapatra, L. Yutao, S. G. Goh, C. Ng, Y. Luhua, N. H. Tran, K. Y.-H. Gin, *J. Hazard. Mater.* **2023**, *445*, 130393; c) J. R. G. Asio, J. S. Garcia, C. Antonatos, J. B. Sevilla-Nastor, L. C. Trinidad, *Emerg. Contam.* **2023**, *9*, 100205; d) M. I. Pariente, Y. Segura, S. Álvarez-Torrellas, J. A. Casas, Z. M. de Pedro, E. Diaz, J. García, M. J. López-Muñoz, J. Marugán, A. F. Mohedano, R. Molina, R. Munoz, C. Pablos, J. A. Perdigón-Melón, A. L. Petre, J. J. Rodríguez, M. Tobajas, F. Martínez, *J. Environ. Manage.* **2022**, *320*, 115769; e) K. Allel, L. Day, A. Hamilton, L. Lin, L. Furuya-Kanamori, C. E. Moore, T. Van Boeckel, R. Laxminarayan, L. Yakob, *Lancet Planet. Health.* **2023**, *7*, e291–e303; f) V. S. Nagtode, C. Cardoza, H. K. A. Yasin, S. N. Mali, S. M. Tambe, P. Roy, K. Singh, A. Goel, P. D. Amin, B. R. Thorat, J. N. Cruz, A. P. Pratap, *ACS Omega.* **2023**, *13*, 11674–11699.

[6] a) A. C. Kogawa, B. G. Cernic, L. G. Domingos do Couto, H. R. N. Salgado, *Saudi Pharm. J.* **2017**, *25*, 934–938; b) D. Bajpai, V. K. Tyagi, *J. Oleo Sci.* **2007**, *56*, 327–340; c) N. Natalie, A. Michael, A. Rogers, *in Encyclopedia of Food Chemistry: Surfactants,* (Eds.: L. Melton, F. Shahidi, P. Varelis), Academic Press, 2016, pp. 2276–2282; dK. Holmberg, in *Ullmann's Encyclopedia of Industrial Chemistry*, **2019**, pp. 1–56.

[7] a) K. R. Harrison, A. D. Kappell, P. J. McNamara, *Environ. Pollut.* **2020**, *257*, 113472; b) P. I. Hora, S. G. Pati, P. J. McNamara, W. A. Arnold, *Environ. Sci. Technol. Lett.* **2020**, *7*, 622–631.

[8] a) M. K. Patel, A. Theiß, E. Worrell, *Resour. Conserv. Recycl.* **1999**, *25*, 61–78; b) J. M. Villota-Paz, J. L. Osorio-Tejada, T. Morales-Pinzón, *Environ. Sci. Pollut. Res. Int.* **2023**, *30*, 34243–34254.

[9] V. Wycisk, M.-C. Wagner, L. H. Urner, *ChemPlusChem.* **2023**, e202300386.

[10] N. Kosaric, F. V. Sukan, in *Biosurfactants*, CRC Press, Boca Raton, **2014**.

[11] a) *J. Am. Oil Chem. Soc.* **1983**, *60*, 1710–1713; b) P. Palfy, B. Marenčíková, *QIP Journal.* **2021**, *25*, 101–119; c) S. Kim, J. Park, *Sustainability.* **2020**, *12*, 4669.

[12] C. A. Boulton, T. M. Lenton, N. Boers, *Nat. Clim. Change* **2022**, *12*, 271–278.

[13] R. Kumar, R. I. Barbhuiya, V. Bohra, J. W. C. Wong, A. Singh, G. Kaur, *Microbiol. Res.* **2023**, *272*, 127386.

[14] A. Gambardella, C. Machado, M. Yunga, J. Diaz, M. Serrano, J. R. Silverman, *RSC Sustain.* **2023**, *1*, 584–591.

[15] V. G. Zuin, I. Eilks, M. Elschami, K. Kümmerer, *Green Chem.* **2021**, *23*, 1594–1608.

[16] a) P. Martens, *BioScience.* **2023**, *biad107*, https://doi.org/10.1093/biosci/biad1107; b) J. Ankrum, *Nature.* **2018**, https://doi.org/10.1038/d41586–41018–05823–41585.

[17] K. Wowk, L. McKinney, F. Muller-Karger, R. Moll, S. Avery, E. Escobar-Briones, D. Yoskowitz, R. McLaughlin, *Palgrave Commun.* **2017**, *3*, 35.

[18] A. Loewa, J. J. Feng, S. Hedtrich, *Nat. rev. Bioeng.* **2023**, *1*, 545–559.

[19] K. T. Savjani, A. K. Gajjar, J. K. Savjani, *Int. Sch. Res. Notices.* **2012**, *2012*, 195727.

[20] B. Y. Feng, B. K. Shoichet, *Nat. Protoc.* **2006**, *1*, 550–553.

[21] C. Qiu, F. Xia, J. Zhang, Q. Shi, Y. Meng, C. Wang, H. Pang, L. Gu, C. Xu, Q. Guo, J. Wang, *Research.* **2023**, *6*, 0148.

[22] a) A. E. Speers, C. C. Wu, *Chem. Rev.* **2007**, *107*, 3687–3714; b) J.-S. Behnke, L. H. Urner, *Anal. Bioanal. Chem.* **2023**, *415*, 3897–3909.

[23] a) E. Gulezian, C. Crivello, J. Bednenko, C. Zafra, Y. Zhang, P. Colussi, S. Hussain, *Trends Pharmacol. Sci.* **2021**, *42*, 657–674; b) H. J. Lee, H. S. Lee, T. Youn, B. Byrne, P. S. Chae, *Chem.* **2022**, *8*, 980–1013.

[24] A. Ganesan, K. Barakat, *MOJ Bioequiv. Availab.* **2017**, *3*, 56–58.

[25] Z. Vinarov, V. Katev, D. Radeva, S. Tcholakova, N. D. Denkov, *Drug Dev. Ind. Pharm.* **2017**, *44*, 677–686.

[26] Y. Lu, E. Zhang, J. Yang, Z. Cao, *Nano Res.* **2018**, *11*, 4985–4998.

[27] C. G. Wermuth, in *The Practice of Medicinal Chemistry (Second Edition)* (Ed.: C. G. Wermuth), Academic Press, London, **2003**, pp. xiii–xiv.

[28] S. Park, H.-S. Ryu, J.-K. Lee, S.-S. Park, S.-J. Kwong, W.-M. WHwang, S.-R. Yun, M.-H. Park, Y. Park, *World J. Clin. Cases.* **2022**, *10*, 2036–2044.

[29] a) T. Ghafourian, A. Nakhodchi, W. Kaialy, in *Surfactants as Penetration Enhancers for Dermal and Transdermal Drug Delivery* (Eds.: N. Dragicevic, H. Maibach), Springer, Berlin, **2015**; b) K. C. Cheng, Z. S. Khoo, N. W. Lo, W. J. Tan, N. G. Chemmangattuvalappil, *Heliyon.* **2020**, *6*, e03861.

[30] M. S. Ostenfeld, M. Høyer-Hansen, L. Bastholm, N. Fehrenbacher, O. D. Olsen, L. Groth-Pedersen, P. Puustinen, T. Kirkegaard-Sørensen, J. Nylandsted, T. Farkas, M. Jäättelä, *Autophagy.* **2008**, *4*, 487–499.

[31] a) P. Pierrat, G. Laverny, G. Creusat, P. Wehrung, J.-M. Strub, A. VanDorsselaer, F. Pons, *Chem. Eur. J.* **2013**, *19*, 2344–2355; b) P. Pierrat, A. Casset, P. Didier, D. Kaereselidze, M. Lux, F. Pons, L. Lebeau, *ChemBioChem.* **2016**, *17*, 1771–1783.

[32] M. Liu, L. Huang, W. Zhang, X. Wang, Y. Geng, Y. Zhang, L. Wang, W. Zhang, Y.-J. Zhang, S. Xiao, Y. Bao, M. Xiong, J. Wang, *Nat. Nanotechnol.* **2022**, *17*, 541–551.

[33] J. P. Overington, B. Al-Lazikani, A. L. Hopkins, *Nat. Rev. Drug Discovery* **2006**, *5*, 993–996.

[34] P. S. Chae, S. G. F. Rasmussen, R. R. Rana, K. Gotfryd, R. Chandra, M. A. Goren, A. C. Kruse, S. Nurva, C. J. Loland, Y. Pierre, D. Drew, J.-L. Popot, D. Picot, B. G. Fox, L. Guan, U. Gether, B. Byrne, B. Kobilka, S. H. Gellman, *Nat. Methods.* **2010**, *7*, 1003–1008.

[35] a) L. H. Urner, I. Liko, H.-Y. Yen, K. K. Hoi, J. R. Bolla, J. Gault, F. G. Almeida, M.-P. Schweder, D. Shutin, S. Ehrmann, R. Haag, C. V. Robinson, K. Pagel, *Nat. Commun.* **2020**, *11*, 564; b) M. T. Agasid, L. Sørensen, L. H. Urner, J. Yan, C. V. Robinson, *J. Am. Chem. Soc.* **2021**, *143*, 4085–4089; c) L. H. Urner, F. Junge, F. Fiorentino, T. J. El-Baba, D. Shutin, G. Nölte, R. Haag, C. V. Robinson, *Chem. Eur. J.* **2023**, *29*, e202300159; d) C. A. Lutomski, T. J. El-Baba, J. D. Hinkle, I. Liko, J. L. Bennett, N. V. Kalmankar, A. Dolan, C. Kirschbaum, K. Greis, L. H. Urner, P. Kapoor, H.-Y. Yen, K. Pagel, C. Mullen, J. E. P. Syka, C. V. Robinson, *Angew. Chem. Int. Ed.* **2023**, *135*, e202305694.

[36] a) L. H. Urner, *Curr. Opin. Chem. Biol.* **2022**, *69*, 102157; b) H.-Y. Yen, I. Liko, W. Song, P. Kapoor, F. Almeida, J. Toporowska, K. Gherbi, J. T. S. Hopper, S. J. Charlton, A. Politis, M. S. P. Sansom, A. Jazayeri, C. V. Robinson, *Nat. Chem.* **2022**,*14*, 1375–1382.

[37] a) N. C. Ghose, D. Saha, A. Gupta, *J. Water Resource Prot.* **2009**, *4*, 290–298; b) P. Verlicchi, A. Galletti, M. Petrovic, D. Berceló, *J. Hydrol.* **2010**, *389*, 416–428; c) N. H. Tran, M. Reinhard, K. Y.-H. Gin, *Water Res.* **2018**, *133*, 182–207; d) S. Top, M. Akgün, E. Kıpçak, M. S. Bilgili, *Water Res.* **2020**, *185*, 116279; e) K. M. Aguilar-Pérez, J. I. Avilés-Castrillo, G. Ruiz-Pulido, D. I. Medina, R. Parra-Saldivar, H. M. N. Iqbal, *Sci. Total Environ.* **2021**, *779*, 146465.

[38] M. Laquaz, C. Dagot, C. Bazin, T. Bastide, M. Gaschet, M.-C. Ploy, Y. Perrodin, *Environ. Sci. Pollut. Res. Int.* **2018**, *25*, 9243–9253.

[39] T. Chonava, F. Keck, J. Labanowski, B. Montuelle, F. Rimet, A. Bouchez, *Sci. Total Environ.* **2016**, *542*, 965–975.

[40] a) M. Petrović, S. Gonzalez, D. Barceló, *TrAC Trends Anal. Chem.* **2003**, *22*, 685–696; b) M. Clara, S. Scharf, C. Scheffknecht, O. Gans, *Water Res.* **2007**, *41*, 4339–4348; c) S. A. Mousavi, F. Khodadoost, *Environ. Sci. Pollut. Res. Int.* **2019**, *26*, 26439–26448.

[41] C. M. Ciamarro, B. F. Pereira, R. M. Da Silva Alves, J. R. T. Valim, D. L. Pitol, F. H. Caetano, *Microsc. Res.* **2015**, *3*, 33–40.

[42] P.-E. Hellberg, K. Bergström, K. Holmberg, *J. Surfactants Deterg.* **2000**, *3*, 81–91.

[43] C. B. B. Farias, F. C. G. Almeida, I. A. Silva, T. C. Souza, H. M. Meira, R. D. C. F. Soares da Silva, J. M. Luna, V. A. Santos, A. Converti, I. M. Banat, L. A. Sarubbo, *Electron. J. Biotechnol.* **2021**, *51*, 28–39.

[44] a) M. Giagnorio, A. Amelio, H. Grüttner, A. Tiraferri, *J. Cleaner Prod.* **2017**, *154*, 593–601; b) M. R. Chirani, E. Kowsari, T. Teymourian, S. Ramakrishna, *Sci. Total Environ.* **2021**, *796*, 149013; c) A. Kumar, A. Kumar, V. Jain, A. Deovanshi, A. Lepcha, C. Das, K. Bauddh, S. Srivastava, *Environmental Sustainability* **2021**, *4*, 447–454; d) C.-W. Zheng, Y.-H. Luo, X. Long, H. Gu, J. Cheng, L. Zhang, Y. J. S. Lai, B. E. Rittmann, *Water Res.* **2023**, *236*, 119944.

[45] A. J. Lawler, V. Ricci, S. J. W. Busby, L. J. V. Piddock, *J. Antimicrob. Chemother.* **2013**, *68*, 1551–1557.

[46] a) L. Amaral, A. Martins, G. Spengler, J. Molnar, *Front. Pharmacol.* **2013**, *4*, 168; b) X.-Z. Li, P. Plésiat, H. Nikaido, *Clin. Microbiol. Rev.* **2015**, *28*, 2.

[47] T. Danevčič, A. Dragos, M. Spacapan, P. Stefanic, I. Dogsa, I. Madic-Mulec, *Front. Microbiol.* **2021**, *12*, 657407.

[48] a) J. Blázquez, A. Couce, J. Rodríguez-Beltrán, A. Rodríguez-Rojas, *Curr. Opin. Microbiol.* **2012**, *15*, 561–569; b) M. Ceragioli, M. Mols, R. Moezelaar, E. Ghelardi, S. Senesi, T. Abee, *Appl. Environ. Microbiol.* **2010**, *76*, 3352–3360.

[49] L. S. Short, V. Lee, R. Mamun, R. Malmberg, L. Li, M. I. Espinosa, K.-I. Abbu, J. Algie, A. Callaghan, P. Cenderawasih-Nere, V. Cullen, M. Gooden, M. Kanoun, A. Lawri, J. Maher, V. Malek, Z. Safdari, B. Shehadie, S.-Y. Shifa, I. Simpson, M. Towns, S. Valter, K. Venkatesan, I. T. Paulsen, *EBioMedicine.* **2021**, *73*, 103653.

[50] T. Lam, Y. Liu, F. Iuchi, Y. Huang, K. Du, Y. Dai, J. Wu, L. Lim, J. Goo, Y. Ishida, J. Liu, J. Xu, *iMeta.* **2023**, *2*, e110.

[51] J. M. Boyce, *Antimicrob. Resist. Infect. Control.* **2023**, *12*, 32.

[52] A. S. Inácio, N. S. Domingues, A. Nunesm, P. T. Martins, M. J. Moreno, L. M. Estronca, R. Fernandes, A. J. M. Moreno, M. J. Borrengo, J. P. Gomes, W. L. C. Vaz, O. V. Vieira, *J. Antimicrob. Chemother.* **2015**, *71*, 641–654.

[53] a) R. Brahma, H. Raghuraman, *Curr. Protoc.* **2022**, *2*, e452; b) H.-Y. Yen, A. Jazayeri, C. V. Robinson, *Pharmacol. Rev.* **2023**, *75*, 397–415.
[54] a) J. P. Hughes, S. Rees, S. B. Kalindjian, K. L. Philpott, *Br. J. Pharmacol.* **2011**, *162*, 1239–1249; b) B. Raymond, *Evol. Appl.* **2019**, *12*, 1079–1091.
[55] B. Plackett, *Nature.* **2020**, *568*, 50–52.
[56] A. R. Collaborators, *Lancet.* **2022**, *399*, 629–655.
[57] a) I. Ogulur, Y. Pat, T. Aydin, D. Yazici, B. Rückert, Y. Peng, J. Kim, U. Radzikowska, P. Westermann, M. Sokolowska, R. Dhir, M. Akdis, K. Nadeau, C. A. Akdis, *J. Allergy Clin. Immunol.* **2023**, *151*, 469–484; b) S. Birant, Y. Duran, T. Akkoc, F. Seyman, *BMC Oral Health* **2022**, *22*, 66.
[58] F. Malek, E. Ranjbari, M. Mirmohammadkhani, D. Pahlevan, *J. Occup. Med. Toxicol.* **2022**, *17*, 6.
[59] G. D. Nielsen, J. B. Nielsen, K. E. Andersen, P. Grandjean, *Int. J. Occup. Environ. Health* **2000**, *6*, 138–142.
[60] T. A. Siebert, S. Rugonyi, *Biophys. J.* **2008**, *95*, 4549–4559.
[61] C. Horwitz, *S. Afr. Med. J.* **1972**, *46*, 1931.
[62] a) G. F. Nieman, C. E. Bredenberg, *J. Appl. Physiol.* **1985**, 129–136; b) K. Saito, K. Orimo, T. Kubo, M. Tamari, A. Yamada, K. Motomura, H. Sugiyama, R. Matsuoka, N. Nagano, Y. Hayashi, K. Arae, M. Hara, M. Ikutani, T. Fukuie, K. Sudo, A. Matsuda, Y. Ohya, S. Fujieda, H. Saito, S. Nakae, K. Matsumoto, A. C. Akdis, H. Morita, *Allergy* **2023**, *78*, 1878–1892.
[63] K. N. V. Palmer, M. D. Camb, *Lancet* **1957**, *269*, 611–613.
[64] U. Kragh-Hansen, M. le Maire, J.-P. Noel, T. Gulik-Krzywicki, J. V. Moller, *Biochemistry* **1993**, *32*, 1648–1656.
[65] U. Kragh-Hansen, M. le Maire, J. V. Møller, *Biophys. J.* **1998**, *75*, 2932–2946.
[66] J.-Y. Maillard, M. Pascoe, *Nat. Rev. Microbiol.* **2024**, *22*, 4–17.
[67] a) M. Chen, S. Xie, *Thorac. Cancer* **2018**, *9*, 1575–1582; b) H. Hong, M. Ji, D. Lai, *Front. Oncol.* **2021**, *11*, 738252.
[68] C.D.M. Wijers, L. Pham, M.V. Douglass, E.P. Skaar, L.D. Palmer, M.J. Noto, *FMES Microbes* **2022**, *3*, xtac016, https://doi.org/10.1093/femsmc/xtac016

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