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Combination of life cycle assessment, risk assessment and human biomonitoring to improve regulatory decisions and policy making for chemicals

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ABSTRACT

Prior to market entry, new chemical substances are assessed for their risk to human health and the environment. Conventional risk assessment (RA) is limited in scope, i.e. it usually does not cover the entire life cycle of a substance, nor does it take into account sustainability aspects such as the amount of raw materials and energy required to produce the substance. Life cycle assessment (LCA) can provide this pivotal information to support an informed decision on the sustainability of a new substance. Unfortunately, LCA has had little regulatory application up to now. We believe that increasing the focus on combined use of LCA and life cycle-based RA could lead to improved regulatory long-term decisions for marketed chemicals. Inclusion of human biomonitoring could increase the robustness of such decisions even further. In addition, the combined use of the three methods allows a robust search for sustainable alternatives of currently marketed chemicals that have an unfavourable risk profile.

1. Introduction

Individuals are constantly exposed to emissions of chemical substances such as nitrogen oxides, formaldehyde and combustion-generated particles. Governments have regulatory measures in place to limit such emissions into the environment or the workplace, and also to minimize the release of substances from consumer products. To develop such measures, authorities require data on emission sources and exposure concentrations, as well as on adverse health effects and potential mitigation options. According to the present chemicals legislation a manufacturer or downstream user "shall consider all stages of the life-cycle of the substance resulting from the manufacture and identified uses" if a chemical safety assessment is required (European Parliament and Council, 2006). Life cycle-based risk assessment (LC-RA) is the most appropriate term to describe such evaluations during the life cycle of chemicals and has been explicitly introduced by various researchers (Christensen and Olsen, 2004; Shatkin and Davis, 2008), though the concept can be implicitly also found in regulation (European Parliament and Council, 2006). LC-RA is used to assess the risks arising from a single substance for a particular use. Industry and regulators scrutinize these risks. However, it is difficult to assess the overall risk of a particular substance, as it may be incorporated into many products, and the total amount of the substance in all products on the market and the frequency of product use is unknown. LC-RA thus gives little to no information about the effective exposure of the population. Approaches that include cumulative exposure assessment and (sub)-populations instead of individuals can partly compensate for the information not provided by LC-RA. Two such approaches are life cycle assessment (LCA), which provides this information on a relative scale (International Organization for Standardization, 2006), and human biomonitoring, which provides concrete exposure values.

LCA evaluates products over their entire life cycle and includes all up- and downstream energy and material requirements with their respective emissions and potential impacts. LCA and LC-RA are often confused, leading to unproductive discussions about the same topic. For example, Life Cycle Analysis (also referred to as LC-RA in Europe) is often used to mean life cycle assessment in the United States. Both approaches have their own strengths, and complementary use of both could improve the regulatory assessment of chemical substances and products. Use of both methods in parallel was first published by (Owens, 1997) and seven years later by (Sonnemann et al., 2004). More recently, successful use of both methods was demonstrated for water quality management (Kobayashi et al., 2015), toluene(Walser et al., 2014) and soy-biodiesel (Milazzo and Spina, 2015). While LC-RA

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of chemicals has already found its way into various regulations, the role of LCA in regulatory decision making is still largely unexplored.

One challenge for regulatory decision making is limited knowledge on cumulative exposure and risk assessment of subpopulations. Regulators receive safety information from industry on individual substances and products, but with vague quantitative information on their use and expected production volumes. Consequently, neither industry nor the authorities have data on the exact use of the substances in the reported products, nor do they know the exact tonnage of substances in similar products. Therefore, estimates of material emissions (and consequently environmental and human exposure arising from industrial and consumer goods in general) are at best fragmented and usually non-existent. National and international initiatives for human biomonitoring (HBM) could fill this gap. In HBM, the concentration of biomarkers in biological samples is measured. Coupled to health data and detailed questionnaires about specific behaviors and potential sources (occupational settings, cosmetic use, lifestyle, dietary habits…), HBM allows to assess the effects resulting from exposure to known chemical substances, taking all sources and routes of uptake into account (Angerer et al., 2007). In contrast to the modelled results from LC-RA and LCA, which follow the pathway *emission – exposure – health impacts*, HBM follows the other direction: starting from observational data – health effects, concentrations in biological samples – the effective exposure can be measured and potential sources identified. Ideally they are quantified by statistical source apportionment (Pleil and Sheldon, 2010). HBM helps to determine critical uses of certain product categories or unsustainable industrial activities. Whereas cross sectional HBM studies give an overview of the chemical burden at a certain time, longitudinal studies that are sufficiently large enable an even more detailed understanding of e.g. potential impacts resulting from existing and emerging chemicals (Nieuwenhuijsen et al., 2006; Clewell et al., 2008). Such longitudinal studies require detailed data and long running times in order to have a value for risk assessment. Data from HBM could help to decide whether regulatory actions are necessary to protect the population or a vulnerable subpopulation from overall exposure.

The regulatory view of the safety or sustainability of a substance, product, or technology can improve with joint use of LCA, LC-RA, and HBM. However, a number of preconditions must be fulfilled prior to implementation and regulatory acceptance. In this article, we present the power of the mutual use of these methods with a focus on LCA, and identify the methodological developments necessary for future regulatory implementation. We illustrate the potential of the three methods with a case study on nanotechnology, which is an emerging industrial sector with a wealth of chemical substances and products for industrial and consumer use.

2. LC-RA in regulation

LC-RA is undoubtedly the principal tool for the regulatory risk assessment of chemicals, and a wealth of literature explains the use of RA in regulatory settings (Traas and Van Leeuwen, 2007). RA starts with hazard identification of the substance, which is subsequently combined with an exposure assessment that may include the environment, work places or households (Paustenbach, 2015). Emissions and transport processes of a hazardous substance must be known to determine the effects upon exposure (dose-response modelling) (Paustenbach, 2015). Responsible production, use and disposal of chemicals require a holistic view on the chemical. Therefore, life cycle aspects are mentioned explicitly in many regulations. A substance-specific risk assessment is a regulatory condition for market entrance in Europe (European Parliament and Council, 2006). The assessments (usually tiered) are determined according to the tonnage, use, and hazards of the new substance. Restrictions may be introduced and classification and labelling are specified for safe use (European Parliament and Council, 2008a,b). The regulations are in principle applicable to all chemicals. For certain chemicals, however, some test guidelines are adapted to capture specific properties. Therefore LC-RA is usually very precise for a specific substance and its use.

3. The added value of LCA

LCA is different to LC-RA and consists of four phases: (1) goal and scope definition, (2) life cycle inventory analysis, (3) impact assessment, and (4) interpretation of the results (Finkbeiner et al., 2006). The scope (1) of the study is usually an environmental and human health assessment of a product or service, either to detect hotspots of concern along the life cycle, or to compare the environmental and human health performance with those of a substitute. One of the outstanding strengths of LCA is that it can cope with a large number of substances being analyzed together and can incorporate transformations along the life cycle of a substance. LCA is good at incorporating models that are not overly detailed; this helps to generate comprehensive results from datasets of hundreds of substances that are not too complex to be handled by an informed person.

Do the environmental and health benefits of a new technology or product outweigh its negative impacts? LCA can provide decision makers with such information on the benefits and impacts over an entire life cycle: LCA considers all material and energy flows involved in the production, use, and disposal of the product, including downstream emissions from the various stages in the life cycle. This part of an LCA is referred to as life cycle inventory analysis (2). The following life cycle impact assessment (3) couples fate-exposure-effect models to quantify potential environmental and/or human health impacts. A distinctive feature of the impact assessment is the effect model, where the toxic effect of a single substance is either normalized to a single surrogate substance or presented as per-capita impact, in order to enable summation of effects from the emissions of all substances of the assessed product system (Guinee et al., 2002). Consequently, the impacts of a substance can be presented in various ways, such as Comparative Toxicity Units (Rosenbaum et al., 2008), or Chloroethylene-equivalents (Jolliet et al., 2003; Goedkoop et al., 2008). The values are relative (i.e. comparative values), since the fate and exposure models are generalized over time and space. The results depend strongly on system boundaries and the comprehensiveness of the inventory. They do not allow conclusions about the absolute safety of a product or process, something that can be done with LC-RA. However, LCA provides a comprehensive assessment of the effects on environmental or human health, with quantitative indicators such as human toxicity, ionizing radiation, ozone layer depletion, or photochemical oxidation.

4. LCA in regulation

The recently adopted action plan for the Circular Economy (European Commission, 2015) covers material flows for entire life cycles: from production and consumption to waste management, with the aim of creating a market for secondary raw materials and thus decreasing emissions and final deposits of unused materials. It shows the increasing political importance of closing material cycles with greater reuse and recycling, which ultimately benefits public health, the environment and the economy. It will lead to adapted regulatory regimes (primarily in the waste sector), which will incorporate life cycle considerations to a higher degree than at present. These life cycle considerations include LCA, which can help to decide on appropriate areas of application for regulatory restrictions of product categories or industrial activities, depending on environmental performance, benefits, and costs. A prime example of implementation into legislation is the requirement of LCA results to evaluate biofuels in Switzerland. The required LCA is an ISO standard and includes an adapted impact assessment method (Frischknecht et al., 2009). The key metrics of this method are eco-factors, which measure the environmental impact of

pollutant emissions or resource extraction activities in eco-points (UBP) per unit of quantity. The more the emissions or use of resources exceed the environmental target (set by the government), the greater the penalty of the impact assessment. Therefore, Eco-points must be updated periodically to stay consistent with the continuously evolving emission situation, new statutory and political requirements. The results have direct consequences for the taxes/subsidies of biofuels in Switzerland (Schweizerischer Bundesrat, 1996). The value of LCAs for political decisions on biofuels was already recognized in 2008 (Scharlemann and Laurance, 2008). A prerequisite for such LCA decision making at the highest political level is the fit-for-purpose approach: political targets need to be implemented in a scientifically robust and fair way, e.g. system boundaries and inventory collection must be comparable between biofuels.

Another example is the European Commission's Energy Labelling Directive, which draws upon results from LCA studies and triggered the introduction of energy labels on electronic products (European Parliament and Council, 2009). Furthermore, the European Waste Framework Directive requires the use of LCA in cases where the waste hierarchy is questionable (European Parliament and Council, 2008a,b).

LCA cannot be used to estimate individual risk. Consequently, LCA studies are of limited use for regulatory decision making where individuals need to be protected. For instance, estimating occupational exposure risks should be addressed separately using health risk assessment, because of local and potentially serious health risks. The same principle applies to the general population or subpopulations that are exposed to potentially harmful substances: LCA results cannot compensate for the need of individual risk estimates. However, information on the magnitude, duration, and number of individual exposures in various environments can be used in life cycle impact assessment. It is a particular strength of LCA that the method does not include thresholds of concern: even the smallest emission is used in combination with exposure and hazard information, and ultimately contributes to an impact factor.

5. Towards implementation of LCA in regulatory decision-making

With international value chains, the environmental impacts of products are global, while regulation is often local – restricted to countries or regions. Therefore, regionalization of LCA results can greatly improve the relevance of LCA in regulatory settings. Regionalized results can highlight spatially resolved environmental hotspots. Many industrial sectors have global outreach. LCAs of entire sectors may provide a broad picture of their environmental performance, but the results may be oversimplified and inaccurate. LCA scenarios help to estimate the environmental benefits and impacts of emerging and future technologies. Such scenarios have limited consequences for regulation today, but they can help to identify innovative products with high environmental or health performance in specific sectors. Scenarios may help to foster safe innovation when the benefits and impacts of products are modelled at an early stage of development. However, this is more policymaking than regulation. Adding weight to LCA in future regulatory settings might be achieved with streamlining and standardization to enable consistent use of LCA. This is particularly true if environmental product declarations (EPDs) and Ecolabels continue to become more relevant for policymakers and regulators. Prerequisites include consistent and comparable goals, scopes and boundaries, which are often deliberately chosen (particularly for recycling calculations). Meaningful functional units as well as consistent and comparable allocation rules for both attributional LCA and consequential LCA are also important.

LCA results can cover multiple impact categories. The selection of these categories and calculation of the impacts must be based on national or international consensus in order to allow comparability and robustness of the results. Data and models for the assessment of human toxicity and ecotoxicity have been consolidated and agreed upon under the umbrella of UNEP-SETAC (Rosenbaum et al., 2008). There are various methods for other impact categories such as water use, and global consensus building is still ongoing. “Best practice” proposals by the European Commission for the use of LCA models are an important step towards standardized use of LCA (Wolf et al., 2012). The American Center for life cycle assessment (www.ACLCA.org) promotes harmonization of LCA models in the US. ISO (International Organization for Standardization) is also active in the development of methodologies, however, without a focus on harmonization. The obvious setback is that relevant and rapid method developments are slow to be incorporated into regulatory LCA. As Hellweg et al. point out, LCA has primarily been used so far for internal corporate decision-making, in particular at an early stage of product and process design (Hellweg and Milà i Canals, 2014). In contrast to such bottom-up LCAs, top-down studies of entire economies can highlight drivers of environmental concern for certain technologies. Such system-wide LCAs can have cross-sectoral informative value. It should not be forgotten that further indicators are needed to broaden the application of LCAs: incorporation of social impacts such as health and safety, human rights, and working conditions would expand our understanding of the impacts of human actions, which was one of the founding concepts of LCA.

Authorities could add more weight to LCA by setting goals for desired future developments in economical, technological, environmental, health or social sectors. Achieving these goals requires policy strategies that permit regular performance checks. Such checks may be provided by LCA and HBM, whose results can be compared with policy goals (see Fig. 1).

For example, an environmental policy might aim to decrease material use and the environmental impacts of building construction by substituting conventional concrete with nano-enabled, lighter concrete with increased strength across a country or region by a given percentage in 2020. If the LCA of the production and use of certain raw materials shows promising results that help to achieve the desired environmental and health benefits, authorities can take this information into account during substance and product evaluations and may even support the introduction of such new materials onto the market (e.g. by subsidies). Confirmation with HBM that levels of a problematic substance are decreasing due to a new health and environmental policy or adapted regulations for consumer products provides even better evidence of the success of these measures.

However, LCA cannot replace regulatory LC-RA because it currently fails to provide specific, harmonized and standardized data on the hazards of an investigated substance. Nevertheless, data from life cycle inventory analysis and results from fate and exposure modelling may be directly used for LC-RA (Fig. 1). A precondition is that international consensus and standardization is reached for emission, fate, and exposure assessment.

6. HBM in regulation

HBM finds its way into regulation indirectly. HBM has primarily been used to monitor chemical substances in biological samples (up to 200) and to detect causalities with health impacts. Such interpretation of HBM data can be used for regulatory risk assessment and management (Wilhelm, 2014). Many national HBM programs are conducted in a cross-sectional manner (GERES (DE) (Umweltbundesamt (Germany), 2016), FLEHS (BE) (Schoeters et al., 2012), CHMS (CA) (Health Canada, 2016), EHMS (CZ) (Černá et al., 2012), NHANES (US) (Center for Disease Control and Prevention (CDC), 2014), etc.). Initiatives such as NaKo (DE) (Nationale Kohorte e.V., 2013), SAPALDIA (CH) (SAPALDIA TEAM, 2015), and Constances (FR) (Zins et al., 2017) partly use HBM results of national cohorts for monitoring and assessing the state of health of inhabitants. Health effects are then correlated to environmental stressors. HBM can inform regulators on the effectiveness of regulatory threshold concentrations for the environment, i.e. whether tolerated environmental concentrations reach

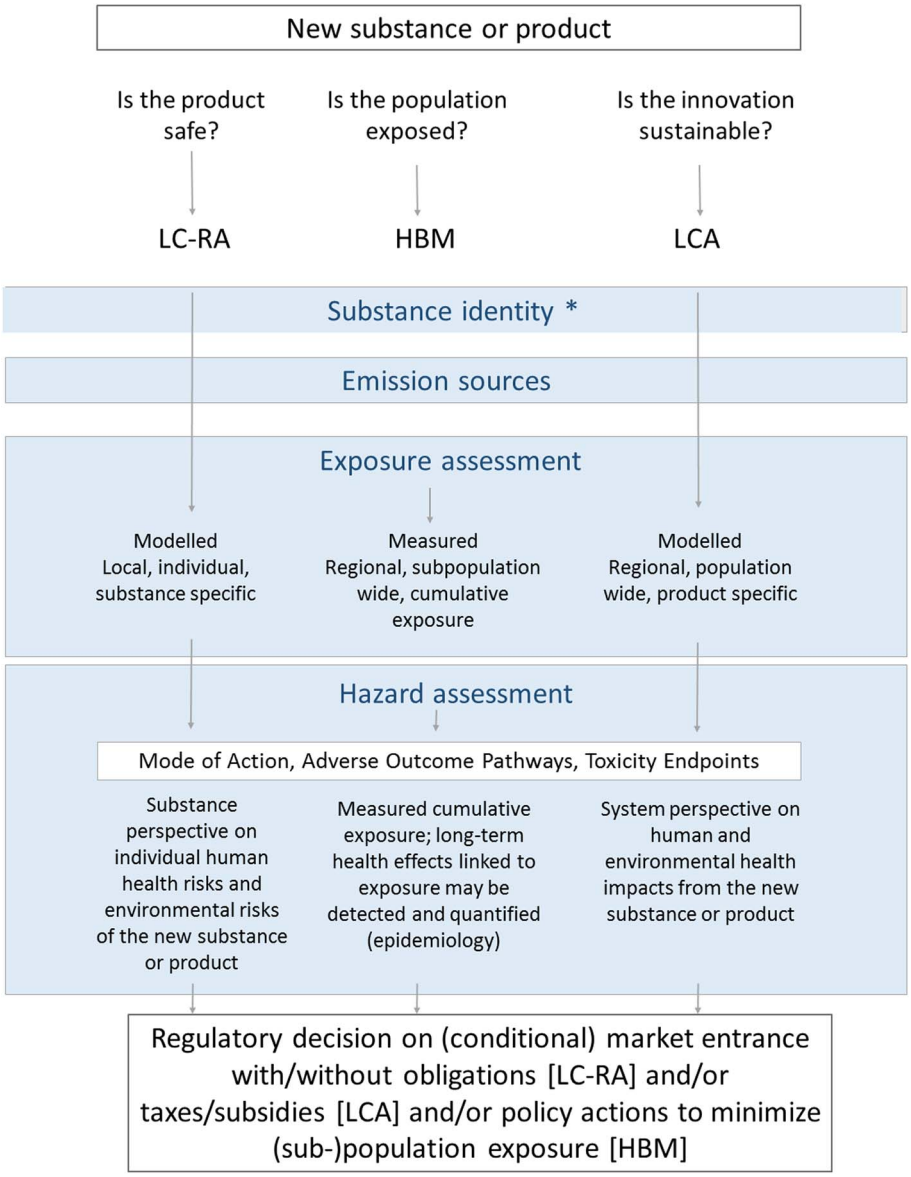

Fig. 1. LCA, LC-RA, and HBM can complement each other for a risk-benefit analysis of a new product. Some data can be used for LCA and LC-RA (e.g. substance identity, emission data and toxicity data) while others require different approaches (e.g. evaluation of toxicity). The added benefits of HBM are the information on measured cumulative exposure while LCA and LC-RA take modelled (summed) single substance exposure into account. The combined results of LCA, LC-RA, and HBM lead to informed regulatory decisions on a substance or product.*Substance identity requires all parameters that potentially contribute to toxicity, which can be difficult for certain materials, such as nanomaterials (size, multielement composition, shape, etc.)

critical doses in humans. It allows one to check the effectiveness of emission reduction policies or shows a need for introducing them. Ideally, HBM complements LC-RA by providing health risk information about the post-use of chemical substances, while LC-RA is used to anticipate potential health risks prior to marketing of the substances.

7. Aligning LCA, LC-RA, and HBM for better regulatory decisions

We show the interactions of LCA, LC-RA and HBM in an example, in which we assume that a new substance or product is being developed (Fig. 1). The producer wants to ensure legal compliance and promising sustainable performance at an early stage of development. A typical question is whether the product is legally safe for employees, consumers, and the environment. This question is answered with LC-RA. Diffuse substance emissions might be detected via elevated substance concentrations in human subjects as determined by HBM studies, after the new substance has been marketed. Furthermore, the producer wants to market a sustainable innovation, i.e. it should be economically viable against competing products and the environmental performance should ideally be better than that of existing products or services. The sustainability aspect can be used as a marketing feature and to reduce costs (e.g. by saving energy) and is typically determined with LCA. A good understanding of the tested substance or product is crucial for the use of LCA, LC-RA, and HBM. Potential emission sources must be identified so that they can be used for the exposure assessment. Comprehensive databases provide LCA background data that should cover processes and associated emissions that extend way beyond the restricted view of one substance only, as is the case with LC-RA. LCA and HBM can therefore provide a broader view of a material with complex pathways and diffuse emissions into the environment than is possible with LC-RA. HBM complements the single substance analysis of LC-RA, by assessing the internal concentration or respective biomarker of a substance from a variety of emission sources. Such data from HBM can supplement the modelling of individual exposure as done with LC-RA. LCA models the cumulative exposure on a population or subpopulation basis (again potentially supplemented with data from HBM). In

contrast to LC-RA, LCA makes use of marginal impacts (no thresholds) and calculates impacts for a population rather than for individuals. This is also true for HBM, where long-term health effects can be detected and quantified epidemiologically. This is virtually impossible with extrapolation from chronic toxicity tests with animal models. LCA and LC-RA sometimes require different levels of toxicity information. For example, a single EC50 of any trophic level can already provide sufficient information in LCA to obtain a toxicity factor, due to transfer and safety factors that allow bridging trophic levels or correlate acute with chronic studies. Moreover, the goal of the toxicity assessment in LCA is to provide a comparative value. Other values such as EC10, NOAEL, or BMD10, for example, have much greater uncertainty in their calculations and are much more conservative than doses that correspond with higher response rates. Thus, for comparative assessments it does not necessarily make sense to compare conservative values, particularly if the uncertainty increases significantly. In contrast, LC-RA are often done according to regulatory rules that apply a tiered approach depending on the hazard profile and the tonnage of a substance as requested by e.g. the Regulation concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals REACH (European Parliament and Council, 2006). The tests for determining physicochemical properties and the toxicity profile follow standardized quality criteria, defined in regulatory relevant test guidelines.

Fig. 2 illustrates a scenario with a combined use of LC-RA, LCA, and HBM that shows their synergistic capacity for a comprehensive safety evaluation of products and substances. The scenario includes three different products (P1, P2, P3) that have assumed identical and constant substance emissions over time. The total exposure is therefore linearly increasing over time (assuming constant elimination, Fig. 2A). In Fig. 2A, Product 3 is added to the emission of Product 2, which in turn is added to the emission of Product 1. Therefore, the cumulative as well as the individual contribution to the exposure can be easily estimated from the figure for any point in time. Below the physiologically determined tolerable body burden, an adverse effect is unlikely. The emission of the individual products P1, P2, or P3 would not have led to an exceedance of this tolerable body burden and therefore would not have been seen as a concern for human health. However, taking a broader perspective with the basket of emitting products P1, P2, and P3, the tolerable body burden is exceeded at time t_y in Fig. 2A, if modelled as part of the life cycle risk assessment. Results of HBM provide measured substance concentrations (or concentrations of the associated biomarkers) from the investigated subjects at different points in time. The regression line determined from the individual measurements provides a temporally resolved substance concentration for the investigated (sub-)population or even an individual. In this scenario, the monitored concentrations are higher at any point in time than the modelled cumulative concentrations from P1–3. This is explained by the fact that P1–3 are unlikely the only sources for the investigated substance. In the scenario, measured concentrations exceed the tolerable body burden at time t_x, which is significantly earlier that the modelled concentrations from the incomplete set of emitting products 1–3.

Fig. 2B investigates Products 1–3 from an LCA perspective. The results of an LCA consider all impacts from up- and downstream emissions of the products. They are shown as time-independent, stepwise increases of impacts with every product added to the scenario. In this case, Product 1 and 2 contribute less to the impacts than Product 3. Impacts can be ecotoxicity or human toxicity, depending on the chosen impact category. The tolerable impact is not necessarily linked to a visible impact and may be defined by e.g. politicians as a desirable goal. If the tolerable impact is exceeded, measures are introduced (e.g. sanctions, taxes, etc.) to bring the cumulative impacts below the tolerated value.

Fig. 2C combines Fig. 2A and B and illustrates the combined explanative power of LC-RA, LCA, and HBM. The tolerable body burden is shown as a two-dimensional area, because this threshold value can be used for both LC-RA and LCA. The red line in Fig. 2C is the connection of individual HBM measurements over time. The total substance release crosses the threshold at time t_x from the onset of emissions (red cross). It shows where the substance concentration exceeds the tolerable body burden. This exceedance depends on the emission rate, environmental fate, and elimination pathways of the substance. The three dimensional shape of the arrow stems from the fact that a measured substance concentration can be integrated into an LCA fate and effect model and therefore contributes to the LCA results.

If policy makers set a goal of a preferred (future) state of the system, it would look like the blue area in Fig. 2C. This blue area should not be exceeded by the cumulative impacts of all products in order fulfil the policy goals. LCA results can highlight emissions from products that contribute substantially to the overall impact, and their minimization would therefore have the highest leverage in improving the system. A reference state is not necessarily a threshold of concern, like as modelled with LC-RA. Of a basket of products, the last product added to the system should not necessarily be replaced first, even if it might be held responsible for crossing the threshold of concern. It would be smarter to sanction the products that contributes most to impacts. Keeping a lifecycle perspective, and including up- and downstream emissions of all inputs into a product, a careful examination of the results of LC-RA and LCA may lead to a policy measure for replacing the product(s) of lowest environmental or health performance with better alternatives.

The results of the combined assessment of the product or substance with LCA, LC-RA and HBM can significantly increase or reduce the willingness for innovation, depending on the sustainability competitiveness of the product or substance. In particular, entirely new substances and products, e.g. nano-enabled applications, can be assessed at an early stage of development for both regulatory compliance and overall environmental performance. From a regulator's perspective, comprehensive assessment of a substance or product with the three presented methods allows a decision that is robust and balanced, and may help to attain sustainability targets strategically, e.g. by introducing taxes, with financial support of promising technologies on the basis of LCA results, or by linking market entry with certain obligations to ensure compliant use of the new product, based on an LC-RA.

8. Illustration of the concept with a nanotechnology case study

8.1. Nanomaterials

Synthetic nanomaterials, manufactured by industries that belong to the emerging sector of “nanotechnology,” provide an ideal showcase for the regulatory use of LCA in combination with LC-RA and HBM. Nanomaterials are usually defined as materials (single particles, agglomerates, aggregates) with at least one dimension below 100 nm (Boverhof et al., 2015). If the nanomaterials are designed to exhibit nanoscale properties, they are usually regarded as “synthetic or manufactured nanomaterials”. Nanoscale properties can be due to increased mobility because of their size, or altered activity due to their higher specific surface area and their morphology. A particular challenge for assessing nanomaterials is that virtually no nanomaterial is the same as any other, and that they transform into many forms along their life cycle, in particular once they are released from the nano-enabled product (Mitrano et al., 2015). Various physical and chemical properties of nanomaterials, e.g. solubility, shape, size, elemental composition and coating, can influence their environmental fate, toxicological kinetics and the biological response upon exposure (Maynard et al., 2006). This is in contrast to chemical substances, which are evaluated on the basis of their molecular structure. The enormous variability of nanomaterials due to the countless possible combinations of their physical and chemical properties requires case-by-case analysis of their hazards. Although nanomaterials are in

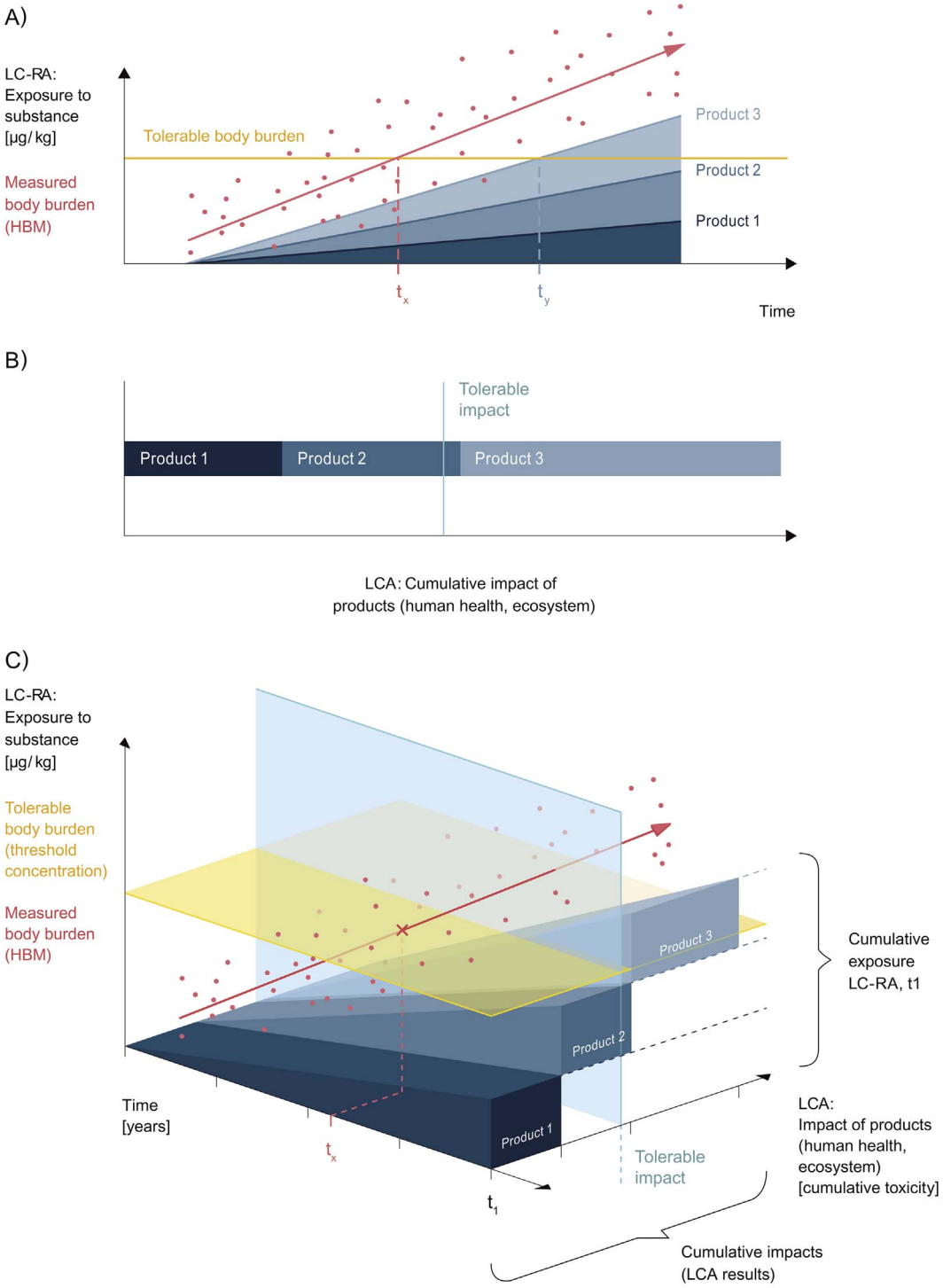

Fig. 2. A and B. The scenario shows three products (P1, P2, P3) with substance emissions assumed to be constant over time, once modelled with LC-RA (A) and LCA (B). Each product contributes with its direct substance emissions to an increased risk for exposed persons, if modelled with LC-RA, and to an increased impact on population health if modelled with LCA. The LCA results include up- and downstream emissions from the products. While the tolerable impact (LCA results) are usually set by policy makers that aim at improving the current state, the threshold concentration is directly linked to the tipping point where health effects become evident. The direct or indirect measurements of the substance in the population with human biomonitoring studies (HBM) lead to a point series which can be linked with a regression line (A). The regression line crosses the threshold concentration (t_x) earlier than the modelled RA concentrations (t_y). Panel C adds the time integrated LCA results to the time dependent LC-RA results and illustrates the combined power of LC-RA, LCA, and HBM in three dimensions on a time scale from zero to t_1. Careful examination of the results of LC-RA and LCA may lead to a policy measure for replacing the product(s) of lowest environmental or health performance with better alternatives. (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.)

principle covered by current chemical regulation, adaptations in the testing strategies and test guidelines are needed. Registrants and authorities are regularly publishing potential solutions to improve the risk assessment of nanomaterials. For example, grouping schemes of similar nanomaterials are being introduced to provide a framework for the identification and grouping of nanomaterials in combination with tailored testing strategies (Walser and Studer, 2015). The many unknowns regarding exposure and effects along the life cycle of nanomaterials can be evaluated with a combination of the methods referred to above: HBM, LCA, and LC-RA. This makes it possible to

address various aspects of nanomaterial applications and improves the overall sustainability assessment of nanotechnology applications.

8.2. Nanomaterials in LC-RA

Depending on national jurisdictions, risk assessments for nanomaterials are conducted either by national authorities or industry, sometimes supplemented with a secondary opinion (e.g. (Scientific Committee on Consumer Safety, 2014). The risk assessment framework for conventional chemicals is considered appropriate for nanomaterials, but adaptations are necessary for exposure models, measurement methods, and test guidelines in order to accommodate nanospecific properties. For instance, nanomaterials have specific transport pathways into the cells and different biokinetics in comparison to other chemicals. Moreover, there is research to be done to determine nanospecific modes of action, such as e.g. redox activity, photoactivation, or inflammasome activation (Nel et al., 2012). New scientific knowledge is continuously monitored by authorities and international bodies. They transform it into regulations and guidelines. An example is OECD, which started to release test guidelines and concepts for grouping and read-across of nanomaterials (Organisation for Economic Co-operation and Development (OECD), 2016). In the near future, nanomaterials can hopefully be tested with a test strategy that allows minimization of testing efforts, while still revealing the relevant toxicities of both simple and complex nanomaterials. LC-RA might be inspired by LCA, where the determined toxicity of a new chemical is compared with a reference substance of well-known toxicity. The toxicity of new substances is then expressed in relation to the reference substance. In LCA, this procedure is called “normalization” and could serve as a guiding principle for LC-RA by introducing relative toxicities (e.g. ranking systems) within or between groups of similar nanomaterials.

8.3. Nanomaterials in LCA

Some reviews and a number of LCAs of nano-enabled products have been published recently, showing the relevance of the widespread use of synthetic nanomaterials and nano-enabled products that have potential emissions to the environment in various sectors (Hischier and Walser, 2012; Walker et al., 2015). The possibility of emissions is associated with concerns about adverse impacts upon human and environmental exposure. A case in point is nanosilver, which is a nanoparticle type used in multiple product categories (paints, textiles, medical products, etc.) and is relevant to various emission scenarios (Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), 2013). Determination of associated *emission – environmental fate – human exposure – impact* pathways is complex, and therefore interactions between HBM, LC-RA, and LCA are useful to retrieve the relevant information for a comprehensive risk assessment. Nanosilver is not found in high concentrations, and a distinction between background concentrations and anthropogenic contributions is almost impossible, which hampers risk assessments of nanosilver at a national or global level (Wijnhoven et al., 2009). LCA can fill this gap because the method can cope with very small long-range effects on health or the environment. The marginal health impacts (on a population basis) of nanosilver (or synthetic nanomaterials in general) are virtually inseparable from the effects of naturally occurring ultrafine particles or other synthetic nanoparticles (and many other human health stressors) in the air. In contrast to LC-RA, LCA can be used to calculate the added impact of a marginal increase in exposure to nanosilver. Moreover, LCA can not only investigate nanosilver related impacts, but can also assess the impacts of other substances that are emitted as a result of the production, use, and waste management of nanosilver products. Nanosilver is a relatively simple nanomaterial, in contrast to more complex nanomaterials with coatings and multi-element composition. LCA has advantages over LC-RA with the grouping of complex nanomaterials for fate and hazard assessment, because higher variabilities are accepted within groups of substances. For instance, currently used LCA models such as USETox still involve variabilities and uncertainties in characterization factors that span a few orders of magnitude, which is particularly true for metals (Jolliet and Fantke, 2015). Therefore, the assessment of nanomaterials might profit from existing knowledge of other substances: nanomaterials share many characteristics with larger particulates, multi-element substances, and certain persistent chemicals. As a result, several methods for the assessment of particulate matter (PM) (Notter, 2015) can support the evaluation of nanomaterials, although traditional LCA methods do not account for the heterogeneity in composition, morphology or surface properties of PM. Conversely, progress in the assessment of nanomaterials might improve the assessment of conventional chemicals.

8.4. Nanomaterials und HBM

Particle-related effects have been observed in cohort studies linking HBM data to health effects (e.g. the SAPALDIA study (Meier et al., 2015)), but nanomaterials have not yet been subject to systematic monitoring. Gonzalez et al. have proposed HBM studies to evaluate genotoxic effects after nanomaterial exposure for workers and the general population (Gonzalez and Kirsch-Volders, 2016). The authors explored the use of common biomarkers for their explanatory power after nanomaterial exposure. A primary field of further research is investigation of the suitability of lymphocytes for analysis after exposure via inhalation and ingestion. Finally, more research is needed on novel biomarkers that are relevant to adverse outcome pathways. A quantitative test for biomarkers that indicate exposure to nanomaterials would enable the early detection of population-wide exposure patterns. Beside the determination of useful biomarkers, the development and standardization of analytical protocols would be a further challenge.

9. Conclusion

LC-RA addresses single substances and products, while LCA provides a system-wide perspective of a product or technology. Both methods require harmonization and standardization in order to obtain appropriate attention from regulators. LC-RA ideally includes the life cycle with production, use and waste management. In contrast to the widespread demand for LC-RA, LCA and HBM have seldom been applied to the regulation of chemicals. This might change in the future because of the complementary value of LCA and HBM. LCA informs regulators of potential environmental and/or health concerns about a product, and provides a unique systems perspective. LCA can provide information on the advantages (environmental and human health) of a new product in comparison to existing substitutes. Likewise, HBM includes the total burden of a substance in individuals, independent of the origin of the emission. If the body burden reaches a critical level as measured with HBM, LC-RA may help to detect the products or economic activities that contribute most to human and environmental exposure for a particular substance. On a coarser level, but with the combination of multiple substances, LCA may point to further critical products or activities. However, since nanotechnology is a multibillion dollar industry with global distribution, LCA can only be used to assess a restricted number of nanotech products. A complete assessment of nanotechnology would oversimplify the results and increase the uncertainties to an unacceptable level. Nevertheless, in contrast to LC-RA and HBM, LCA can help to identify innovative nano-enabled products with high environmental performance in specific sectors.

Subsequently, effective policy measures such as promotion of more sustainable products and technologies or restrictions for problematic product categories or industrial activities, may reduce human exposure. Longitudinal HBM can verify the efficacy of regulatory actions.

For a comparative and holistic view of the environmental and health performance of a product or system, authorities may profit from

combined use of LC-RA, LCA, and HBM. Such an analysis is not limited to products already on the market – it can also be used to compare the sustainability of a product in the development stage with that of existing or new products as it has been illustrated with the case study of nanotechnology. The combined use of the three methods can lead to an informed strategic prioritization of safer chemicals, improved waste management, and lowered human exposure that can be implemented at an early stage of product marketing. This is of particular importance in view of the increasingly strict environmental and chemical regulations that are aimed at making the use of chemicals healthier for all.

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