Incorporating Principles of Green Chemistry in R&D Programs

Reimagining USEPA Sustainable Futures Models as Core Tools in the Commercialization Process

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- Kelly is a Principal Consultant at ERM. She spent 15 years at the USEPA serving as a technical expert on the use of predictive models to assess environmental fate, hazard, and exposure concerns for industrial chemicals under the Toxic Substances Control Act (TSCA). In her consulting work she supports regulatory strategies for the introduction of new industrial chemicals in North America and helps clients develop safer chemistries by incorporating hazard, exposure and risk considerations early in the research and development stage.

Scenario – Decision Time

Capital project for a new chemical.

6 mo. R&D cycle thanks to great chemists.

Voice of the customer – indicative of strong demand year over year.

Business case presented to leadership team.

Investment	Cash Inflow				
Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
(1,000,000)	250,000	500,000	500,000	750,000	1,000,000
Company Expectations				**Business case**	
Payback period = 3 years				Payback period = 2.5 years	
Net Present Value (NPV) = positive return on capital				NPV = 1,150,000	

Result:

Failed to consider product stewardship in the decision and needed to be addressed after the investment:

- Doesn’t meet customer expectations for greener chemistry
- Hazard profile identified as toxic – limited market interest resulting in reduced cash inflow
- Regulatory restrictions promulgated due to solvent emissions
- Deemed to fail company criteria for investment after-the-fact

New Paradigm for Chemical (Product) Development

Product stewards can play a key role in R&D developing “greener” products.

12 Principles of Green Chemistry

- ✓ Pollution Prevention
- ✓ Atom Economy
- ✓ Less Hazardous Chemical Syntheses
- ✓ Designing Safer Chemicals
- ✓ Safer Solvents and Auxiliaries
- ✓ Design for Energy Efficiency
- ✓ Use of Renewable Feedstocks
- ✓ Reduce Derivatives
- ✓ Catalysis
- ✓ Design for Degradation
- ✓ Real-time analysis for Pollution Prevention
- ✓ Inherently Safer Chemistry for Accident Prevention

What is the company "green chemistry" perspective?
Which lever(s) can you pull?

Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University Press: New York, 1998, p.30.

Stage-Gate(R) Product Development

Can we make it "green"?

What are the PS implications?

Does it meet our standards for "green"?

Will this meet the needs of the customers?

Why is R&D stage most important

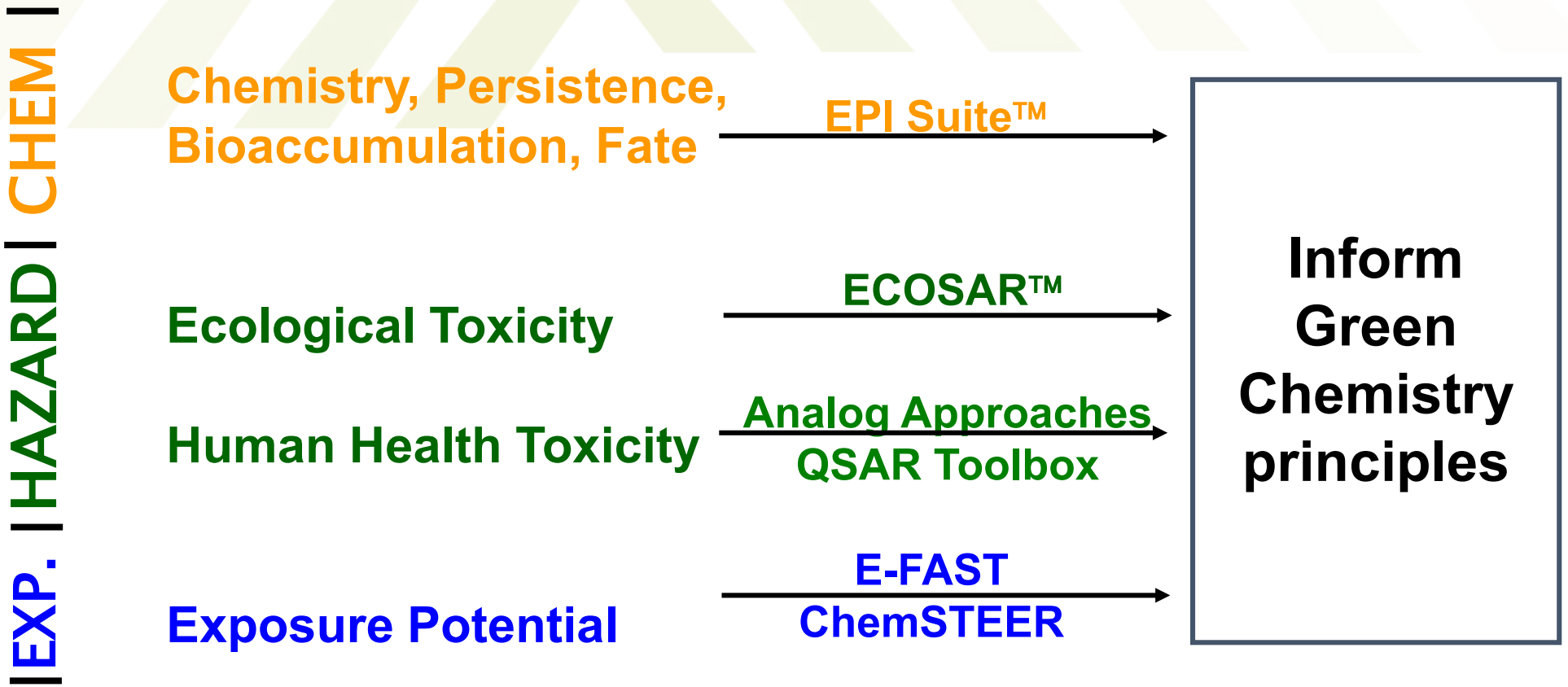
- Identify issues sooner before large capital investments
- Early enough to mitigate business risk
- Sustainable business practices – stakeholder expectations
- Most flexible phase, changes, not committed

There are tools the product steward can utilize to help inform R&D on greener chemistry parameters`

Tools for Screening at R&D

- Computerized predictive methods have made significant advances over the last 20 years and can be used to:
  - Identify safer substitution opportunities – or – benchmark against replacement to assess viability
    - Avoid regrettable substitutions!
  - Address hazard and risk concerns early in chemical development
  - Implement emerging sustainability initiatives
    - “Safer and Sustainable by Design”
  - Inform targeting testing strategies to best utilize resources

USEPA Sustainable Futures Tools



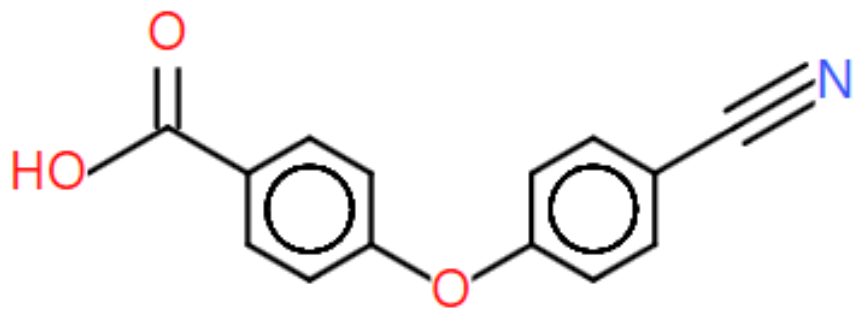
Other Predictive Models and Tools

- Other tools available to assess hazard, exposure and risk
  - Commercial programs can be expensive to license, but they can be valuable in supporting decision-making
- Use of the same tools applied by regulatory authorities covers the intersection of both green chemical design ***and*** chemical regulation
  - Anticipate regulatory hurdles by applying the same tools, approaches and assumptions approving agencies will use during new chemical registration

What is EPI Suite™?

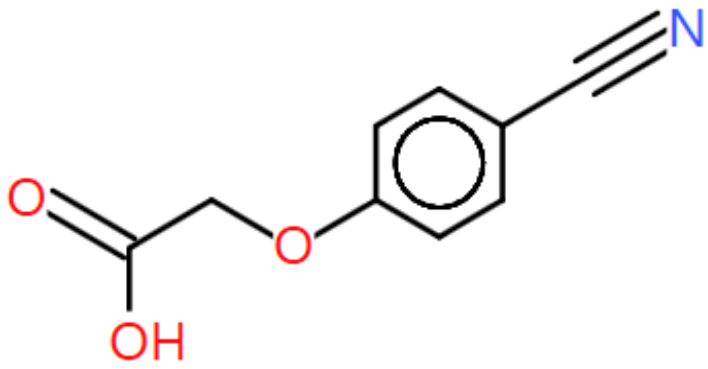
- **E**stimation **P**rograms **I**nterface **Suite**
  - https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface
- **Provides**
  - Physical-chemical properties and environmental fate estimates for a molecule to inform the basic physical nature of a substance and potential degradation pathways
- **Gives insight into questions like:**
  - Once released, will the chemical go to air, water, soil, or sediment?
  - How long will substance persist in each of those environmental compartments?
  - Is the substance going to be bioavailable to present toxicity concerns?
  - How might humans and the environment be exposed to the chemical?

P-Chem/Fate Properties Informing Green Chemistry



- Low Solubility
- Sticks to soil and sediment
- Not readily biodegradable
- Persistent in environment

-Versus-



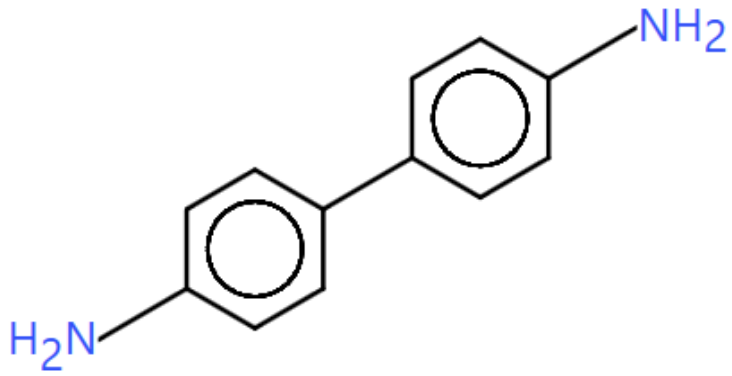
- Water Soluble
- Biodegradable
- Not persistent

Green Chemistry Principle: *Design for Degradation*

What is ECOSAR™?

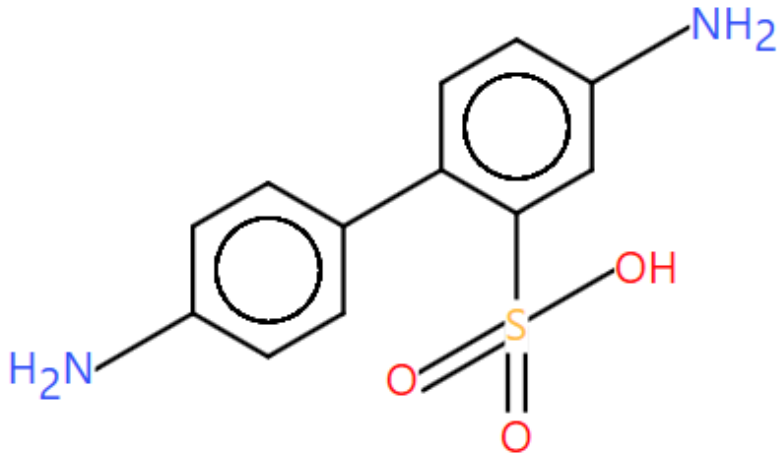
- **Ecological Structure Activity Relationship Model**
  - https://www.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model
- **Provides**
  - Acute and chronic toxicity estimations for aquatic organisms
    - For industrial chemicals, the major media of concern are generally freshwater bodies
- **Gives insight into questions like:**
  - Should we design our process to minimize release of the chemical to water?
  - Does the chemical pose hazards to multiple trophic levels (aquatic plants, invertebrates and vertebrates)?
  - Is there testing that could be conducted to help fill data gaps or to better characterize the ecological hazards?

Ecological Toxicity Informing Green Chemistry



- Low solubility
- Moderate Kow
- Very toxic to aquatic organisms

-Versus-



- High water solubility
- Low Log Kow
- Low aquatic toxicity

Green Chemistry Principle(s): Designing Safer Chemicals and Inherently Safer Chemistry for Accident Prevention

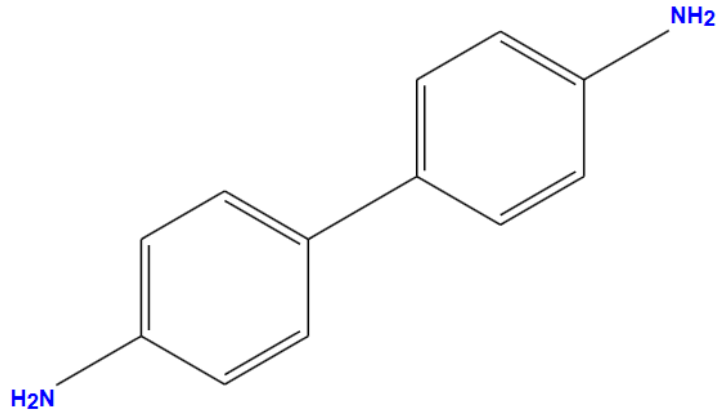
Human Health (Mammalian Toxicity) Approaches

- Due to the predictive complexity of cancer and non-cancer endpoints, the scientific community has largely focused on the use of analogs and read-across approaches
- The assessment of potential toxicity can incorporate several factors:
  - **Physicochemical Factors**
    - Molecular weight
    - Physical state
    - Solubility
    - Chemical reactivity
  - **Metabolic Factors**
    - Blocking of detoxification
    - Enhancement of activation
  - **Electronic and Steric Factors**
    - Resonance stabilization
    - Steric hindrance
    - Molecular size and shape

Human Health (Mammalian Toxicity) Approaches

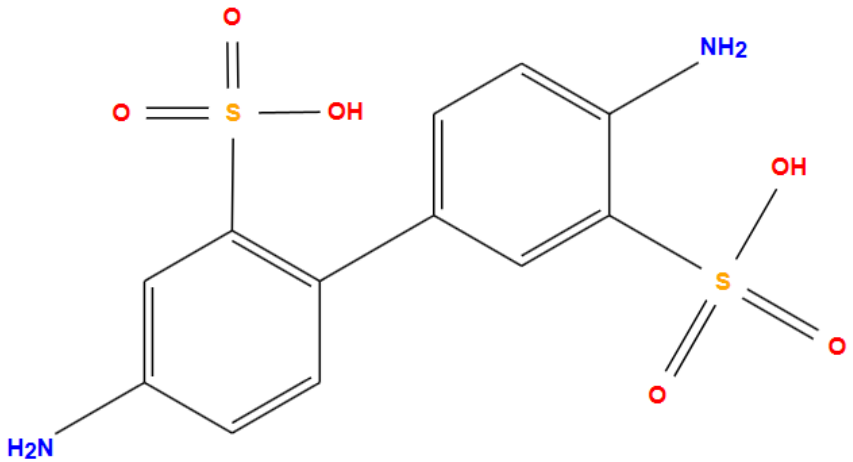
- **OECD QSAR Toolbox**
  - http://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
  - Described as a tool to facilitate “analog analysis” and chemical grouping to maximize predictions using various read-across techniques
- **Provides**
  - Information on potential human health hazard concerns and a quantitative basis for the risk assessment
- **Gives insight into questions like:**
  - What adverse effects might this chemical cause?
  - Should we conduct targeting testing to fill data gaps?
  - What molecular design changes could we make to lower toxicity concerns?

Human Health Toxicity Informing Green Chemistry



- Known carcinogen
- Acute and chronic mammalian toxicity concerns

-Versus-



- Render molecule more water-soluble to reduce absorption and accelerate excretion
- Make amines (NH_2) less reactive by adding electron withdrawing groups
- Significantly lowers toxicity concerns

Green Chemistry Principle(s): Designing Safer Chemicals and Inherently Safer Chemistry for Accident Prevention

What is ChemSTEER?

- **Chem**ical **S**creening **T**ool for **E**xposures and **E**nvironmental **R**eleases
  - https://www.epa.gov/tsca-screening-tools/chemsteer-chemical-screening-tool-exposures-and-environmental-releases
- **Provides**
  - Worker exposure and environmental release concentrations based on supply chain. Evaluates physical form of chemical, waste disposal practices, transportation methods, etc. using EPA exposure models and default assumptions
- **Gives insight into questions like:**
  - Can we make changes to the operations to reduce releases or exposures?
  - Should we be protecting workers from specific exposure activities of concern?
  - What type of PPE or engineering controls should we use for a particular process?

Physical Form and Exposures in the Supply Chain Informing Green Chemistry

Handle as dried solid or powder

- Significant worker inhalation concern
- Triggers need for PPE respiratory protection program and training
- Potential for product loss during operations through dusting

-Versus-

Handle as wet cake or formulate into non-volatile liquid

- Exposure limited to dermal contact
- More easily addressed with PPE (gloves)
- Limited product loss from vapors or dusting

Green Chemistry Principle(s): Designing Safer Chemicals and Inherently Safer Chemistry for Accident Prevention

What is E-FAST?

- **E**xposure **F**ate **A**ssessment **S**creening **T**ool
  - https://www.epa.gov/tsca-screening-tools/e-fast-exposure-and-fate-assessment-screening-tool-version-2014
- **Provides**
  - Subsequent general population and ecological exposure estimates from industrial, commercial and consumer activities in the supply chain
  - Comparision of various waste disposal methods to identify associated concerns based on the media of release (e.g. air or water).
- **Gives insight into questions like:**
  - What activities in the supply chain could potentially pose unintended risk to the general or ecological population
  - What are the best approaches to managing waste disposal for the chemical of interest

Disposal Methods in Supply Chain Informing Green Chemistry

Aquatically toxic chemical disposed via incineration

- Significant energy consumption for process
- May still pose risk based on incomplete incineration and high hazard concern
- Expensive to implement along supply chain

-Versus-

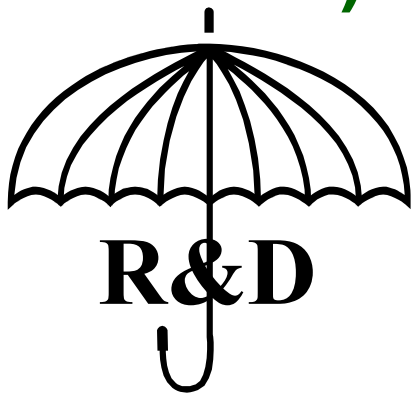
Non-toxic and biodegradable chemical disposed to local wastewater treatment

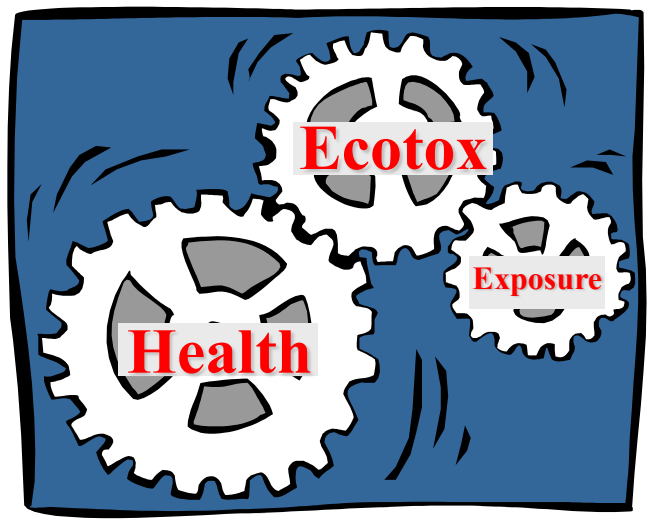
- Lower energy consumption for disposal
- Overall ecological risk mitigated *via any disposal method* due to low toxicity
- Allows more flexibility in disposal methods

Green Chemistry Principle(s): Designing Safer Chemicals and Design for Energy Efficiency and Pollution Prevention

Chemical Screening at R&D

EPA Sustainable Futures Models (and others)





Satisfied Customer

Business Benefits

Greater regulatory certainty for commercial introduction

Case Study: Example in Action

R&D chemist – I have a great idea!

- New molecule with an ester functionality is going to solve all our company problems compared to the incumbent chemistry.
- Scalable from the bench, initial performance looks good
- Production economics look feasible

It’s "greener“ right?

Case Study: Context Setting

CAS No.	Submitter:
PHYSICAL/CHEMICAL PROPERTIES:	
Melting Point (deg C)	
Boiling Point (deg C)	
Boiling Point Pressure (mm Hg)	
Vapor Pressure (mm Hg)	
Water Solubility at 25 deg C (g/L)	
Log K_{ow}	
ENVIRONMENTAL TRANSPORT AND FATE:	
Transport	
Henry's Law Constant – HLC (atm-m^3/mol)	
Soil Adsorption Coefficient – log K_{oc}	
Log Bioconcentration Factor – BCF	
Persistence	
Probability of Rapid Biodegradation	
Ultimate Biodeg Model	
Primary Biodeg Model	
Ready Biodegradability (MITI Model)	
Atmospheric Half-life	
Hydrolysis Half-life	
Volatilization Half-life for Model River	
Volatilization Half-life for Model Lake	
Removal in STP (EPA Draft Method)	
Experimental Data	
Byproducts	
Degradation Products	
Metabolites	

- Gather data and organize in context of EPA's Sustainable Futures workbook (dated).
- Interpret results based on EPA guidance, policies, and practices.
- What are the company expectations?

Case Study: Results

Concern Level	HIGH	MODERATE	LOW
Persistence	Half-life in soil & sediment > 60 days		
Bioaccumulation	Considered bioaccumulative BCF >= 1000		
Cancer Health Hazard		Structural alert for nongenotoxic carcinogenicity	
Non-Cancer Health Hazard		Structural alert for “strong” estrogen receptor binding	
Aquatic Toxicity Hazard	Acute aquatic values < 0.1 mg/L Chronic aquatic values < 0.1 mg/L		
PBT criteria?	YES		

- Model endpoints and summarize results in EPA Sustainable Futures format.
- Hazard concerns were identified.
- Informed decision making – kill the project.
- Post-mortem – Molecular attributes of concern highlighted.

Evolution of the Business Case

Categorization	Expectation
Financial Performance	Company requirements - e.g., payback period, cash flow, etc.
Green Chemistry	Are we addressing and can we quantify an attribute(s) demonstrating our commitment to green chemistry?
Product Sustainability	How does the product fit into the company goals and objectives?
Circular Economy	How does the product fit into the company narrative for circular economy requirements?
Decision Point	What is the totality of the business case presented in the assessment?

Question

Are these concepts part of your company's commercialization process currently?

Thank you

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