Why Clarification of Ethical and Legal Challenges Associated with Emerging Technologies Is a Hard Problem

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… as one variation on biosafety work with
J. Christopher Anderson and colleagues at UC Berkeley

Outline:

I. **Understanding one aspect of the ethical and policy challenge associated with emerging tech:**
   Sparse information and residual risk

II. **The case study**: develop software that radically deskills design of Microbial Chemical Factories

III. **The contribution**: a generalizable strategy for for managing residual risk with sparse information

Residual Risk

An emerging technology poses a novel risk when:

(There is a reasonable basis for thinking) there is (may be) a nontrivial risk of harm to humans (or other animals and plants upon which humans depend) that remains after current infrastructure for managing risk has been deployed.

Note: residual risk is a function of both the emerging technology and the current infrastructure

Determination of residual risk requires:

1. A **novel technology** or technological capacity
2. that is a variant of a **conventional type**
3. in an **anticipated context of use**
4. with a specified **risk scenario**
5. in relation to an **existing policy infrastructure** for managing the conventional type
6. to determine the **unmitigated risk**
7. so the infrastructure can be extended to mitigate that type of risk

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… AND we want to avoid polarization between precautionary and risk based allocation of burden of proof for providing the information required for traditional risk analysis

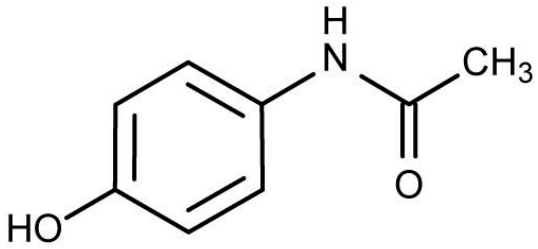
This is a hard problem:

- **At least as difficult as the R&D** associated with the emerging technology, since it requires that expertise to realistically appraise the technical novelty
- **Irreducibly interdisciplinary**, and thus cannot be allocated to any one disciplinary domain
- Requires **appreciation of the scope and limits of hard and soft regulatory infrastructure**; this is rarely possessed by any single individual
- **Requires collaboration** between disciplines with very different interests and languages, and which often have histories of suspicion and conflict

II. Case study: **Residual risk in synthetic biology**

1. The novel technology: **Microbial Chemical Factories (MCFs)**
2. The conventional type: **recombinant DNA research**
3. Anticipated context of use: **university lab**
4. Risk scenario: **unintended generation of novel pathogen**
5. existing policy infrastructure: **NIH guidelines** and Institutional Biosafety Committees
6. unmitigated risk: **risk** of unintended generation of novel pathogen **when MCF research is handled as BSL-1**
7. so the infrastructure can be extended to mitigate that type of risk: specification of pathway associated with risk scenario allows **mitigation with sparse information**

New | Lasso | Eraser | Single | Template | Carbon | Charge | Center | Reaction | Peptide | Ink | PubChem



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1. The novel technology: MCFs

    * deskills design
    * maps possibility space of design

    * can generate BSL-2 risk group
        with BSL-1 parts

2. Conventional type: recombinant DNA research
3. Context: university lab
5. Policy infrastructure: IBCs and NIH Guidelines

Step 1: identify Risk Group of parent agent and sources of sequences

Step 2: ask if new biosafety risk arises from synergy of sequences leading to novel phenotype

But no guidance on what kind of a novel phenotypic trait is relevant for determining Risk Group.

Biosafety Level (BSL): gives a relative measure of risk posed by an agent to its environment, and thus gives levels of precaution when working with these agents in an enclosed facility.

BSL-1: well characterized agents not known to cause disease in healthy humans or pose risk to environment; e.g., non-pathogenic E. coli (MG1655). Modest precautions.

BSL-2: agents that cause mild, treatable disease or are difficult to transmit in aerosol form; e.g., Lyme disease, Salmonella, mumps, measles. Precautions involve higher levels of training, constrained access to lab when experiments conducted, protective clothing, etc.

BSL-3 and **BSL-4**: Agents that cause severe/fatal disease, treatable or untreatable; e.g., TB, anthrax for BSL-3; Ebola and hemorrhagic fevers for BSL-4. Highest precautions.

The **risk management heuristic** used by synthetic biology researchers: determine Biosafety Level by considering the Risk Group of parent agent and any parts.

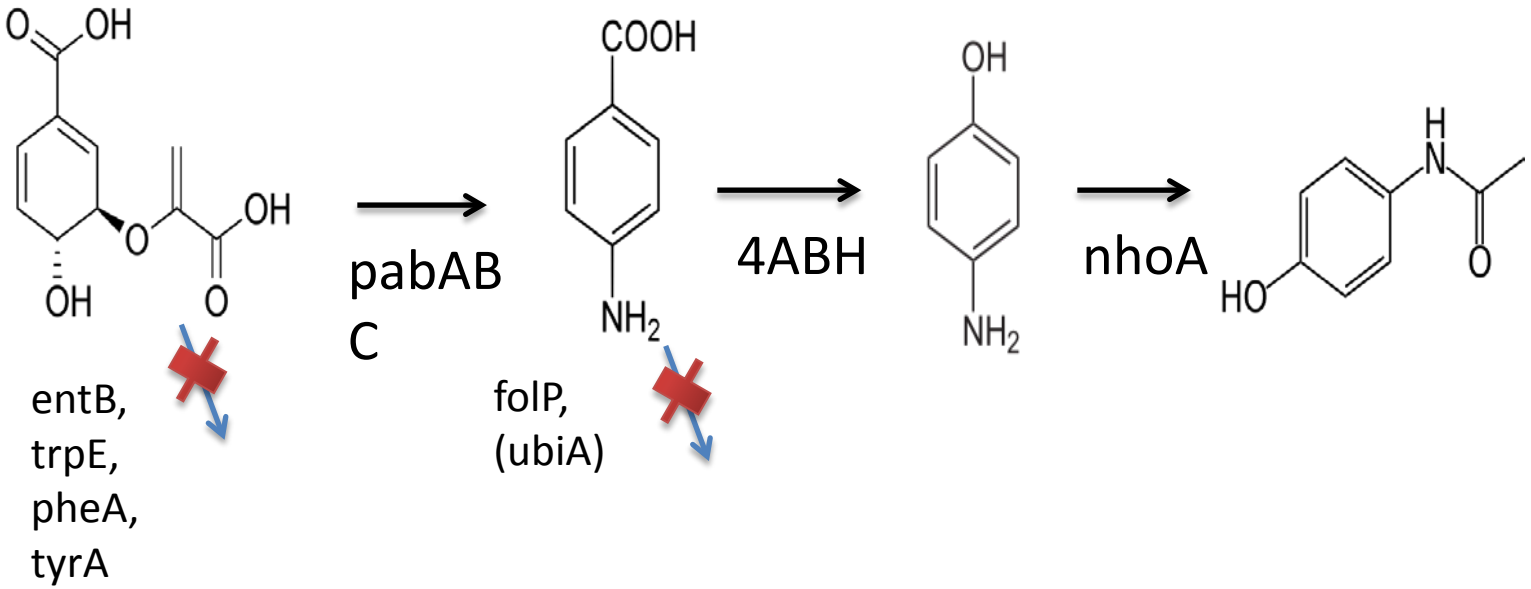
4. The risk scenario: pathway for unintentional generation of a novel pathogen

1. Wild type contamination of experiment → 2. plasmid uptake leading to MCF target produced → 3. colonization of researcher →

4. Production of toxic levels of MCF target → 5. Transmission of wild strain MCF to other humans

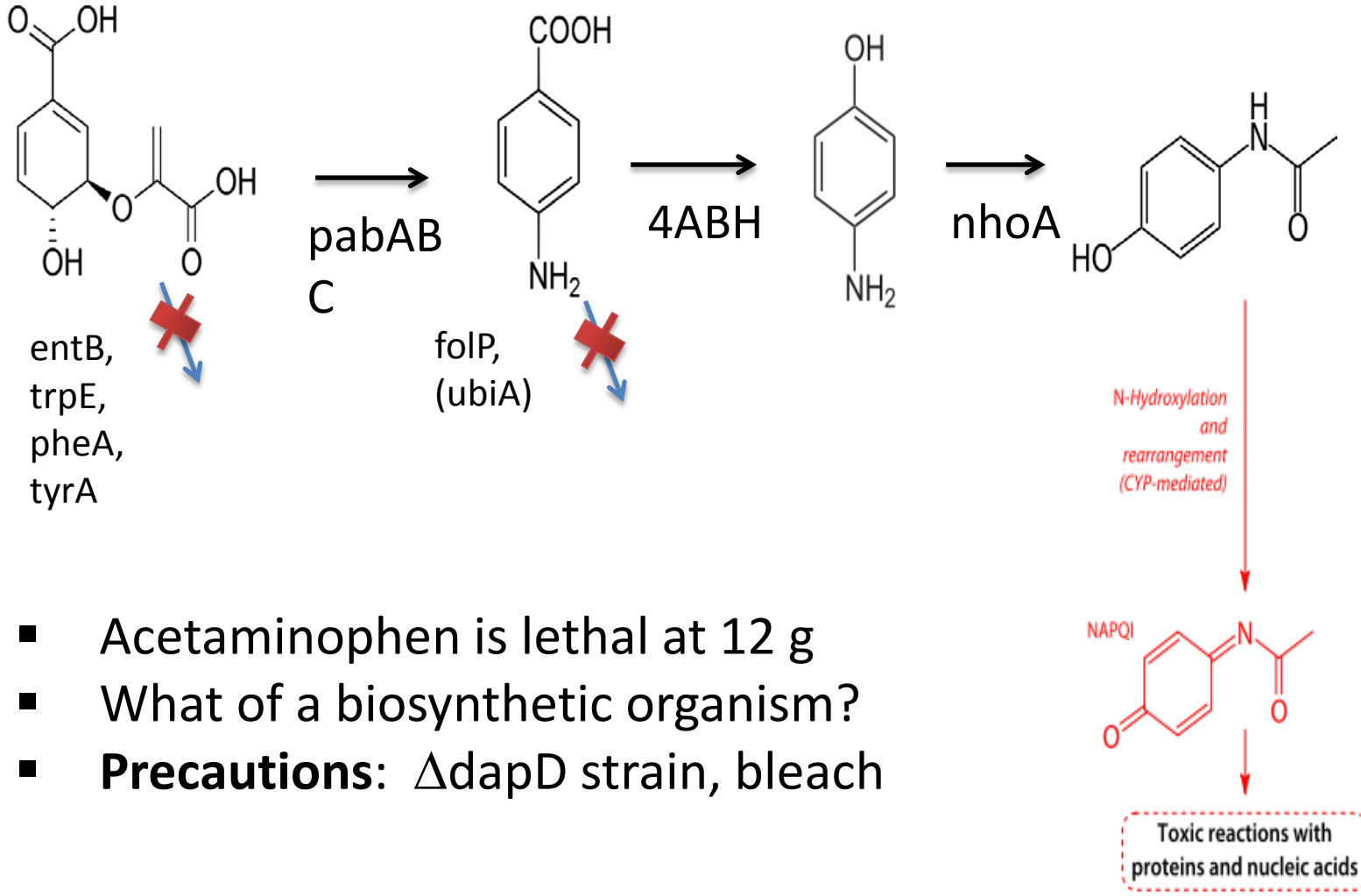
Novelty of phenotype that matters for risk scenario: toxic level of anything in pathway leading to MCF target

6. Residual risk associated with Tylenol production pathway:



In sum: according current wisdom for managing biosafety, this can all be handled with precautions associated with BSL-1.

Why Tylenol-producing E. coli should NOT be regarded as a BSL-1 agent:



- Acetaminophen is lethal at 12 g
- What of a biosynthetic organism?
- **Precautions**: ΔdapD strain, bleach

7. The risk mitigation pathway: any node in pathway!

1. Wild type contamination of experiment → 2. plasmid uptake leading to MCF target produced → 3. colonization of researcher →

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Novelty of phenotype that matters for risk scenario: toxic level of anything in pathway leading to MCF target

Biosafety issues associated with the Act example:

(1) **Non-project-specific Risk: The insufficiency** of current biosafety levels for managing risk associated with synthetic biology **does not first arise with Act** and its discovery of Tylenol-producing E. coli. This is already a problem, but one that has not been appreciated. **Act discloses a systemic gap** between current syn bio research and the regulatory infrastructure for managing that research. While additional instances of the new type of risk might arise with Act (e.g., quantitative increase of the risk), this project does not introduce the new type.

(2) **Project-specific risk**: Act does introduce or exacerbate some risks in such a way that we can identify a **distinctive type of emergent risk associated with this project**; e.g., by deskilling the design process, Act makes it possible for a much broader group of people to develop pathways that can generate products of interest in target organisms. Some of these individuals will not recognize the emergent risks in the way a senior researcher would. Thus, **by virtue of the way it deskills, Act increases the likelihood that an unknowledgeable person may create something dangerous** that previously could only be created with much effort by highly skilled research teams.

(Note some fuzzy boundary between these categories.)