Algal Biofuels
Practical Perspective - Regulatory
(from the standpoint of a legal practitioner)

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Federal investment in algal fuel technology development is significant

- ***$24 million*** federal investment in algal-based fuels
  - In 2010, the DOE awarded $6 million to Arizona State University for the creation of the Sustainable Algal Biofuels Consortium (SABC), $9 million to the University of California, San Diego for the creation of the Consortium for Algal Biofuels Commercialization (CABC), and $9 million to Cellana LLC Consortium in Kailua-Kona, Hawaii.
- Supplemented by substantial private investment: Cellana LLC, for example, raised around ***$100 million*** in capital on top of its DOE grant.
- Additionally, there are currently ***more than 100 academic efforts*** to modify and refine algae into fuel.

Source- *Algae: Fuel of the Future?* *Maybe, but not because of government subsidies*
http://www.nationalreview.com/articles/292913/algae-fuel-future-nash-keune
March 8, 2012

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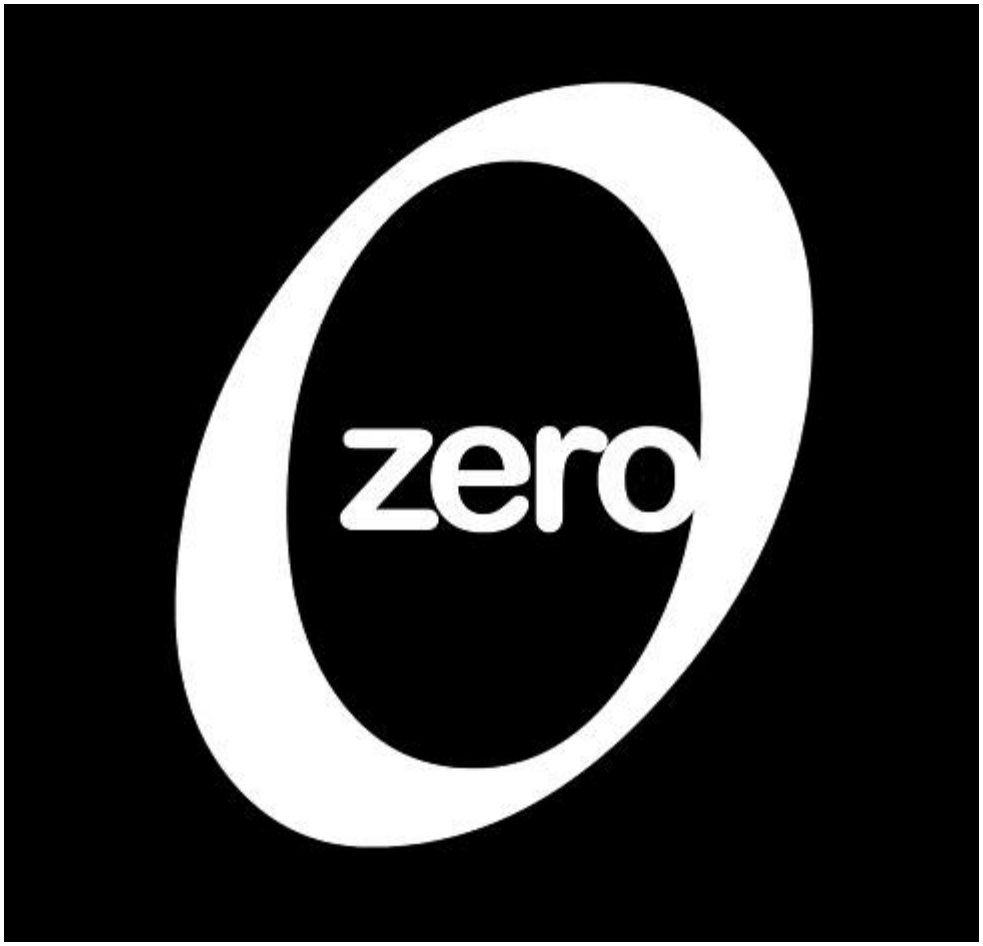
Number of public EPA TSCA clearances for algae production strains for fuels



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Why?

- Microalgae are still in the process of being discovered, understood, optimized….and modified
- Taxonomy is under development, subject to change, poorly understood
- What to call a strain affects its TSCA regulatory status and possibly the TSCA status of the product it is making
- No good exposure assessment modeling currently exist to quantify releases

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TSCA information needs -

- **Sufficient information** to make a reasoned evaluation of health and environmental effects
- In the absence of sufficient information, EPA can regulate if it finds that
  - manufacture, processing, distribution, use or disposal *may present* an unreasonable risk of injury to health or the environment; or
  - substantial quantities *may reasonably be anticipated* to enter the environment or there may be significant or substantial human exposure

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TSCA notification considerations

- Each modification of an intergeneric strain is a change that most likely requires EPA review
- It is virtually impossible to guarantee or achieve zero release, particularly in open pond systems, but there is no good way to estimate the extent or effect of projected releases of viable cells
- If you have a benign (non-toxic) strain, should zero release be expected?
  - Is the replacement of one species by a competing species in a particular habitat an unreasonable risk of injury if the ecosystem is not harmed and the species being replaced exists elsewhere?

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Addressing notifications – short term

- Design:
  - Start with benign recipient strains and use sequences from benign intergeneric donor strains
    - Established through evaluation of the public literature at species level if possible
  - Use modification techniques that do not create a new TSCA notification obligation
- Data:
  - Develop kill curve and comparative growth data at a minimum to accompany notification

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Benign by design

- EPA emphasis is on toxin sequence, rather than the use of the source organism
  - However, if sequence can be obtain from a non-listed source, this is preferred rather than having to defend why it is not going to be a problem.

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Benign by design, cont.

- For EPA, “free of toxin encoding sequences” means
  - Introduced genetic material must not contain a functional portion of any of EPA’s listed toxin encoding sequences at 40 C.F.R. § 725.421(d)(2).
    - “Functional portion” means any sequence which codes for a polypeptide that directly or indirectly contributes to toxic effects in humans.
  - Binds a toxin or toxin precursor to target human cells
  - Facilitates intracellular transport of a toxin in target human cells
  - Similar or identical sequences isolated from organisms other than those listed.

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Toxin sequence examples

- Direct –
  - A sequence whose encoded polypeptide is directly toxic to target cells, e.g., the portion of diphtheria toxin that inhibits protein synthesis.
- Indirect –
  - A sequence whose encoded polypeptide is not directly toxic to target cells, yet still adversely affects humans, e.g., the portion of botulism toxin that blocks release of acetylcholine.

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Additional lists to determine toxin encoding sequences

- HHS and USDA under the National Select Agent Program, regulate nucleic acids that can produce infectious forms of Select Agent viruses and nucleic acids that encode for toxins. (**www.selectagents.gov**).
- Lawrence Livermore National Laboratory (LLNL) Virulence database (**http://mvirdb.llnl.gov/**)
  - This includes protein toxins, virulence factors, and antibiotic resistance genes
  - Combines databases from eight different public-access sources updated weekly
    - Tox-Prot (subset of the Swiss-Prot database)
    - SCORPION (scorpion toxins)
    - PRINTS (virulence factors)
    - VFDB (virulence factors)
    - TVFac (toxins and virulence factors)
    - ARGO (vancomycin and b-lactam antibiotic resistance genes)
    - VIDA (animal virus)
- UniProtKB for animal toxin and venom proteins. (**http://www.uniprot.org/program/toxins/**)
- CDC and university databases on toxins of biological origin

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TSCA notification needs for certain modification techniques

Methods used to introduce genetic modifications	Considered and regulated by the U. S. E.P.A
Physical mutagenesis (UV, X-rays, gamma rays, particle radiation)	**No**
Chemical mutagenesis (alkylating agents and azides)	**No**
Chemostat evolution and selective breeding	**No**
Heat shock/ electroporation	**Yes if the coding regions are intergeneric**
Viral or bacterial vector-mediated (such as Agrobacterium)	**Yes if the coding regions are intergeneric**
Biolistic (gene gun)	**Yes if the coding regions are intergeneric**
Microinjection	**Yes if the coding regions are intergeneric**
Cell fusion or cell hybrids	**Yes if the coding regions are intergeneric**
Insertion of intrageneric sequences (such as overexpression, rearrangements, or deletions of endogenous genes) using modern biotechnology techniques	**No. EPA does not require notification of intrageneric modifications;**

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Current risk assessments

- Can be based on published literature for parental and donor strains
  - Must be able to show that modifications do not alter behavior in a manner that would not permit reliance on parental strain
  - If behavior is different, may need to conduct testing to address effects of the change in behavior
- Increasingly there is bias to test the strain
  - Faster review time may be the benefit that outweighs the risk and cost of testing

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Longer term regulatory considerations

- Consider proposing a “well-characterized” or “bad bug” list approach for expedited decision making
- Engage in stakeholder and government funded efforts at the genus level to characterize health and safety of key microalgae that show promise for fuels
  - Consider pathogenicity testing on representative strains and the development of exposure modeling tools for aerosol releases
- Encourage EPA to consider programmatic approaches to R&D to maximize development and production during optimum growing seasons
- Encourage efforts to expand internal agency expertise

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Current assessment – strain regulatory

- There is insufficient development of information on algal taxonomy, strains, and expected releases
- Insufficient information leads to conservative risk assessment decisions
- Conservative risk assessment decisions do not allow new fuels to compete with existing ones
- Then the fruits of these investments are not realized
- It is time to consider EHS investment needs for this technology

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Current assessment – product regulatory

- More conventional and likely to clear faster than the production strain, however, trouble spots to try and address include –
  - EPA policy for biological strains and their products is to give them source-based names, but every modification does not necessarily make a new chemical
    - Should not need a new PMN each time the construct is simply further optimized
  - Significant quantities of fuel production can lead to transportation and equipment clean out release estimates that present aquatic toxicity concerns

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Thank You

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