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RFI Response: Potential Changes to the Policies for Oversight of Dual Use Research of Concern (DURC) and the Potential Pandemic Pathogen Care and Oversight (P3CO) Policy Framework

White House Office of Science and Technology Policy
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The Center for Security and Emerging Technology (CSET) at Georgetown University offers the following comments to the Office of Science and Technology Policy (OSTP) in response to the Request for Information on *Potential Changes to the Policies for Oversight of Dual Use Research of Concern (DURC) and the Potential Pandemic Pathogen Care and Oversight (P3CO) Policy Framework*.

We appreciate the opportunity comment on the important task of evaluating and updating the DURC and P3CO frameworks into a streamlined biosecurity and biosafety policy. We commend the USG for inviting expert feedback from the NSABB[1] and through this RFI as it considers potential changes. We hope to add to this discussion with our following comments, informed by our recent CSET report *Understanding the Global Gain-of-Function Research Landscape.*[2] Based on our research for this paper, during which we manually reviewed a representative sample of nearly 500 research publications that fit our criteria of gain- or loss-of-function research and observed that this research encompasses a range of experimental approaches, study designs, and potential outcomes that result in different levels of risk, we suggest the following considerations for future biosecurity policy.

Expanding the scope of research regulated by DURC and P3CO and development of a risk-based assessment framework (Questions 2b, 2c, 3b, and 3c).

While much of the discussion to date has rightly focused on high-risk research that could harm human health, our analysis identified a broad swath of foundational scientific research that is not high-risk. Future regulations should be carefully fine-tuned to apply to the highest-risk research of concern without unduly interfering with research that is unlikely to cause harm.

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[1]National Science Advisory Board on Biosecurity. "Proposed Biosecurity Oversight Framework for the Future of Science." March 2023. https://osp.od.nih.gov/wp-content/uploads/2023/03/NSABB-Final-Report-Proposed-Biosecurity-Oversight-Framework-for-the-Future-of-Science.pdf

[2]Schuerger et al. "Understanding the Global Gain-of-Function Research Landscape." Policy Brief. Center for Security and Emerging Technology, August 2023. https://cset.georgetown.edu/publication/understanding-the-global-gain-of-function-research-landscape/.

Specifically, two findings from our report should be considered when designing a risk-based framework for pathogen research oversight:

1. **Unique combinations of low, medium, and high-risk elements contribute to a study's overall risk level.** A major challenge in developing a risk assessment is that risk occurs along a spectrum and that there is no clear border to definitively separate "benign" from "concerning" research. For example, a study's potential risk will change based on factors like the pathogen's biosafety level (BSL) and the degree of physiological similarity between research animals and humans. This spectrum of factors is unique for each study; two studies that are in the same category for one risk factor might be in different categories for another. Furthermore, these risks can be additive. A study may not contain any individual "high-risk" elements, but instead contain multiple "moderate" risk factors that combine into a high-risk outcome. Future risk assessments should address each study's unique combination of individual risk factors instead of relying on a few criteria to fully categorize risk.
2. **Experimental outcomes and their associated risks are difficult to predict.** Biological systems depend on complex, interconnected networks of molecular pathways that fluctuate based on environmental and genetic factors. This complexity can make it difficult to predict the impact of a single genetic change. Nearly one-third of the publications in our analysis resulted in both gain- and loss-of-function outcomes, highlighting the interconnected nature of mutations that increase versus decrease virulence. Even with robust preliminary data, experimental conditions do not perfectly replicate biology and studies can yield unexpected results. Additionally, a genetic mutation that causes one effect under a certain set of experimental conditions may cause the opposite effect under other conditions. For example, one of the studies in our analysis generated a mutated virus that replicated more efficiently in cell culture (GOF), but was less pathogenic in mice (LOF). Extending these results to predict the physiological response in a human would add another layer of uncertainty. Similarly, serial passage can either increase or decrease pathogen fitness depending on the host cell type or animal and selection conditions. These examples highlight the real-world difficulties in predicting experimental outcomes for biological pathways that are not fully characterized. When experimental outcomes are unpredictable, evaluating which experiments are risky is difficult to predict as well. To account for this unpredictability, future risk assessments should be multifaceted and should not solely rely on predicted experimental outcomes to identify high-risk studies.

An approach accounting for both of these challenges could involve a risk assessment matrix that enumerates multiple potential risk factors, including *both* experimental factors and predicted outcomes. These two categories are both important to identify potentially risky studies, but neither alone fully accounts for the variability inherent in scientific research. By considering individual experimental and predicted components, reviewers may identify potentially risky combinations of factors that wouldn't be recognized otherwise. Some criteria for each dimension include:

- **Experimental factors** might include the initial pathogen's risk characteristics like biosafety level (BSL), risk group (RG), and infection route, or experimental methods like serial passage, which may increase or decrease function in unexpected ways, or animal use, which may be accompanied by expanded host range or the risk of animal-to-human transmission. If applicable, studies that propose to add, delete, or modify pathogen genes should also consider the gene's function and other characteristics. Importantly, studies that include any of these factors should not be immediately interpreted to be "risky," but should instead be given extra care to identify combinations of materials and methods that may result in a more virulent pathogen. Final criteria for such a risk assessment should be developed with input from virologists, immunologists, epidemiologists, and public health experts.
- **Predicted outcomes** are still a valuable component of a risk assessment strategy. However, more clarity is needed to determine what counts as "reasonably anticipated" including a description of what level of expertise is required to predict an outcome, what level of certainty these predictions should have, and how much consensus there must be between experts. Oversight should also account for the possibility that studies that are not predicted to result in an enhanced pathogen may nevertheless do so. A notification structure to report unanticipated results and continued oversight throughout the research lifecycle should be included in future policies, in agreement with NSABB Recommendation 4.1. We encourage OSTP to solicit and implement guidance from technical experts when considering updates to the 7 experimental outcomes described in the DURC policy or within the definition of ePPP described in P3CO.[3]

A matrix-based risk assessment could provide more standardization while still accounting for the spectrum and combinatorial nature of risk, and be incorporated into university biosafety programs. By identifying risk factors early, researchers can proactively prepare risk/benefit analyses and draft risk mitigation plans, similar to the current process of institutional and investigator involvement in DURC oversight. These increased researcher and investigator responsibilities will require additional technical and financial support, as discussed in the following section.

Such an approach will need to clearly describe which combinations of factors correspond to which outcomes, which could include enacting additional biosafety measures or escalation to HHS department-level review. Many of the studies that contain elements within the risk matrix will likely not merit additional review, and these research proposals should not be described as "risky" or painted with a broad brush.

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[3]The United States Government, "United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern", September 25, 2015, https://www.phe.gov/s3/dualuse/Documents/durc-policy.pdf; National Institutes of Health. "Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens." 2017. https://www.phe.gov/s3/dualuse/Documents/P3CO.pdf

Impact of expanding investigator and institutional responsibilities and necessary resources for implementation (Questions 1b, 2a, and 2e)

Involving investigators and institutions earlier in the research lifecycle can increase transparency and clarity while streamlining the review process, by identifying research that is potentially subject to review early and collecting relevant risk information, like risk assessments, risk/benefit analyses, and risk mitigation plans, before proposal submission. As an added benefit, including investigators in the risk assessment phase may encourage researchers to recognize and change specific elements of their studies during the research design phase to reduce risk.

While expanded institutional and investigator roles can positively impact the review process, these additional responsibilities will also significantly increase workload. We support the NSABB's Recommendations 4, 5, and 8 that the USG should clearly articulate investigator and institutional roles, responsibilities, and expectations, provide educational, training, and implementation materials and guidance, and designate a governmental office to provide financial and technical support. Increased institutional responsibility will likely necessitate additional personnel. Financial assistance and resources should be provided to ensure that logistical burdens do not discourage institutions from pursuing research projects. Clear guidance for investigators and institutions should be developed to help researchers understand, interpret, and implement the matrix-based risk assessment, similar to the Companion Guide for DURC implementation.

In addition to expanded investigator and institutional workloads, a matrix-based risk assessment will likely also increase the federal workload for review and oversight because it will cast a broader net and identify more studies that contain potential risk factors. To prevent this increased scope from delaying or hindering research, the government agencies that oversee this work should also be expanded with additional resources and personnel.

Removal of blanket exclusions for research associated with surveillance and vaccine development (Question 5)

Balancing the benefits of this research with biosafety concerns is a major challenge in evaluating exemptions for surveillance and vaccine development. However, while it is complicated, guardrails can and should be developed that are grounded in a better understanding of what research is actually going on and what benefits are likely gained from it. Such guardrails could foster developments in these areas while ensuring safe research conduct, potentially make the topic less polarizing. As highlighted in CSET's study, since gain- and loss-of-function research are often intertwined and the outcomes of experiments are not knowable beforehand, exempting some studies from oversight leaves a gap in the regulatory framework.

We agree with NSABB's Finding 3 which states that research should be assessed based on its potential to result in an enhanced pathogen rather than the reason or context for conducting the research. The removal of current exemptions is unlikely to affect the majority of public health research, as our findings also support the second key insight from the American Society for Microbiology's *Impact Assessment of Research on Infectious Agents*[4] that the highest-risk research makes up a very small fraction of biological research.

We found that gain- and loss-of-function research is widely used for public health applications, including vaccine development (24% of identified publications). However, we also found that the riskiest categories of research were infrequent—for example, fewer than 1% of publications were conducted on pathogens categorized as BSL-4. This result suggests that very few of the identified vaccine development studies would be subject to regulation as "high-risk" research under a matrix-based approach. An assessment that accounts for the varying types and ranges of risk could help to differentiate the truly risky studies from those that are less likely to cause harm.

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A policy research organization within Georgetown University, CSET provides decision-makers with data-driven analysis on the security implications of emerging technologies, focusing on artificial intelligence, advanced computing, and biotechnology.

[4]"Impact Assessment of Research on Infectious Agents." Workshop Summary. American Society for Microbiology, September 2023. https://asm.org:443/Reports/Impact-Assessment-of-Research-on-Infectious-Agents.