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Inclusion of digital sequence information under the scope of the Nagoya Protocol

Dear Mrs Paşca Palmer,

German Life Sciences Association (VBIO e. V.) is pleased to accept the invitation of the CBD secretariat to submit views and relevant information concerning the ongoing discussion on the possible inclusion of digital sequence information (DSI) under the scope of the Nagoya Protocol.

We kindly ask to take into account our following concerns:

1. The very challenging definition of the regulation subject DSI will lead to legal and regulatory insecurities.
2. Biodiversity research will be impeded, thus negatively affecting conservation of biological diversity.
3. Fair and equitable sharing of benefit will be compromised.
4. The inclusion of DSI will assault the special considerations of the Nagoya Protocol (Art. 8).

You will find our views in detail as well as recommendations attached.

For queries and further information, we are happy to provide additional input from our Association or its scientific experts.

Yours sincerely,

Prof. Dr. Bernd Müller-Röber
President VBIO

Dr. Kerstin Elbing
Dep. Science & Society

Implications of the Inclusion of Digital Sequence Information under the scope of the Nagoya Protocol

The German Life Sciences Association VBIO e. V. (Verband Biowissenschaften, Biologie und Biomedizin in Deutschland) is Germany's largest association for life sciences. It represents about 30,000 members spanning the entire spectrum of the biological sciences, from the molecular and cellular to the organismic and ecological levels, and includes the biomedical field.

We understand and agree that there is an ethical requirement to have a clear framework for sharing the real (monetary or non-monetary) benefit arising from the access to, and the use of, genetic material. However, the move towards adding Digital Sequence Information (DSI) under the scope of the Nagoya Protocol is not the appropriate way to respond to these ethical concerns.

Indeed, it has been shown that the Nagoya Protocol is based on concepts of biological diversity that are mostly inapplicable in certain fields of research, especially in microbial research. Due to this incongruence, the Nagoya Protocol threatens future microbial research, potentially defeating its original purpose[1].

Similar effects are likely to occur if DSI is included under the scope of the Nagoya Protocol: DSI have an entirely different character than physical genetic resources and the legal definition of the regulation subject itself is highly sophisticated, indeed, our four major concerns are:

(1) The inclusion of DSI will create unnecessary and difficult-to-overcome barriers to research including the research on global biodiversity.

(2) It will harm a mayor basis of the objective of the Convention on Biological Diversity (CBD), namely the conservation of biological diversity.

(3) We expect that another main objective of the CBD - the fair and equitable sharing of the benefits arising from the utilization of genetic resources – will be compromised too.

(4) The inclusion of DSI will assault the specific considerations outlined in Art. 8 of the Nagoya Protocol.

Therefore, we kindly ask the Ad Hoc Technical Expert Group on DSI to take into account the following concerns:

1. The very challenging definition of the regulation subject DSI will lead to legal and regulatory insecurities

During the negotiation process of the Nagoya Protocol, it was extensively discussed whether digital sequence information obtained from a genetic resource should be considered to fall under the term "genetic resources". The agreed definition of a "genetic resource" refers to Article 2 of the CBD (also cited in Nagoya Protocol Article 2 c). Accordingly, a genetic resource is "genetic material (means: any material of plant, animal, microbial or other origin containing functional units of heredity [i.e., genes]) of actual or potential value". Thus, intangible digital sequence information is not covered by the fundamental definitions of CBD and Nagoya Protocol yet. Any approach to include DSI in the scope of the Nagoya Protocol

[1] Overmann, J. & A. Hartman-Scholz (2017): Microbial Research under the Nagoya protocol: Facts and fiction. - Trends in Microbiology, February 2017, Vol. 25, No. 2: 85-88. http://www.cell.com/trends/microbiology/fulltext/S0966-842X%2816%2930164-0

post hoc has to start with a mutual agreement on an accurate, reliable and applicable terminology of the regulation subject (DSI) itself. Due to the particular character of DSI compared with (physical) genetic resources this definition will be very challenging.

The precondition for any sharing of any benefit - which may arise at a later point - will be the proof of the "identity" or "uniqueness" of a genetic sequence which has to be traced back to the specific (physical) genetic resource from which the genetic sequence originated in a specific provider country.

On the one hand, sequence identity may be very high in organisms – especially microbes -- scattered throughout the world. Recent whole-genome analyses of geographically separated microbial strains have confirmed high sequence identity of up to 99%[2]. Other studies of bacterial strains from very different habitats from both hemispheres (distance: 18,000 km) revealed similar gene content (up to 93%), and identical secondary metabolites[3]. Which country would in such a scenario be the "country of origin" and have the rights over the resulting DSI? And by which technical procedures and regulatory mechanisms can the origin of the organism be proven? How can this be traced if no physical object is involved?

On the other hand, there are specific differences in sequences of the same species from the same habitat, which are caused by natural mutations. These variations of genetic sequences might occur very often and in short time – especially in microorganisms. Additionally, genetic recombination in sexually reproducing organisms leads to genetic sequences that show considerable differences between individuals.

These sequence variations occur in all DNA regions irrespective as to whether the distinguishing region is of interest to the researcher or whether a potential benefit may result at a later point in time. Therefore, the definition of a "unique" genetic sequence for the purpose of precision in legislation and regulation under the Nagoya Protocol is likely to be fraught with complexity: Would a "unique sequence" in regulatory categories be one that does not have a 100% identical match to any entry in the current public databases? Or would 0.1% sequence divergence, or a single nucleotide difference between organisms be sufficient to declare "uniqueness" and thereby justify a claim by the provider country? And, more importantly, how can this information have a chain of custody and be securely tracked by authorities? These practical and scientific considerations alone should be sufficient to reject the inclusion of DSI.

Unlike many biological samples, DSI can be reused indefinitely. If DSI were to be included under the scope of the Nagoya Protocol, this could result in an ever increasingly complex picture involving multiple agreements on benefit sharing for any given genetic sequence, which would be "attached" to the sequence forever, with each further transfer requiring additional permission and documentation resulting in long-term and increasing litigation burden, financial and time delays to research and innovation. Deposition of DSI in (public) databases is currently mandatory for every scientist publishing research results obtained by using DSI. This precondition is fundamental to scientific transparency and verifiability of the results. Uncomplicated access to DSI is important to trigger new scientific hypothesis and therewith scientific progress.

However, no system is yet in place that ensures uncomplicated access and reliable tracing of a sequence that is ultimately employed for profit generation. None of the so far proposed

[2] Speth, D.E. et al. (2012) Comparative genomics of two independently enriched 'Candidatus Kuenenia stuttgartiensis' anammox bacteria. Front. Microbiol. 3, 307. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3423927/pdf/fmicb-03-00307.pdf

[3] Thole, S. et al. (2012) Phaeobacter gallaeciensis genomes from globally opposite locations reveal high similarity of adaptation to surface life. ISME J. 6, 2229–2244. https://www.nature.com/ismej/journal/v6/n12/pdf/ismej201262a.pdf

solutions for monitoring and tracing DSI - the contract model, and the copyright and database right model - provides a perfect solution[4].

If DSI will be included under the scope of the Nagoya Protocol, a researcher has to assure in advance that all relevant legal and regulatory requirements are met for each single sequence he up- or downloads from a data repository. This procedure might be practicable for few DSI – but research in life sciences often needs a bulk of different DSI for comparison to gain high-quality, reliable and solid results. Filing agreements to get legal access to each single sequence and/or database throughout the research process represents a substantial administrative burden and will unnecessarily delay or even prevent scientific research.

2. Biodiversity research will be impeded, thus negatively affecting conservation of biological diversity

Conservation of biodiversity relies on broad knowledge, which is at least partly created through scientific research on the inventory of genes, species, their interactions, their functionality and services they provide to the ecosystem.

Today, the investigation of DSI is an integral component of species identification and/or taxonomy. Often, DSI is essential for surveying the diversity of organisms, when morphological identification is difficult to achieve or simply not possible (e.g. in cases like: detection of invasive species, detection of protected species, identification of morphologically cryptic species).

Information on genetic diversity encoded in DSI is also widely used to support conservation research on DSI which supports understanding the genetic structure of populations or species and thereby provides important additional information that helps to ensure effective conservation management of genetic diversity, or to target sampling for the establishment of *ex situ* collections to support conservation *in situ*.

The broad use of DSI also contributes to sustainable use of biodiversity as it for examples provides otherwise unaccessible information on pollinator conservation[5] or the role of genes that control plant growth, development and stress tolerance in different climates and their resilience to environmental change.

Thus, the availability of sequence data for comparison of species, subspecies, ecotypes or accessions is key to reaching the Aichi biodiversity targets, namely strategic goal C (to improve the status of biodiversity by safeguarding ecosystems, species and genetic diversity), especially target 13, and strategic goal E (to enhance implementation through participatory planning, knowledge management and capacity building), in particular target 19.

Undoubtedly, the wider and comprehensive use of DSI strongly supports a far better understanding of Earth´s biodiversity and its dynamic changes. The utilization of DSI thus provides a superior knowledge base that will facilitate the implementation of the CBD. However, this toolbox can only be effectively employed if as many DSI as possible are accessible with low financial and regulatory burden. The evidence base for conservation planning and implementation of the Convention would be damaged, if DNA sequencing itself is unduly restricted by the Nagoya Protocol or if the procedures to access DSI are costly, technically restricted or highly regulated.

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4 Lawson, C. & Rourke, M. (2016): Open Access DNA, RNA and Amino Acid Sequences: The Consequences and Solutions for the International Regulation of Access and Benefit Sharing. Griffith Law School Research Paper No. 16-12. 43p available under: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2848136

5 Shalene J., M. M. López-Uribe, A. Soro (Ed.) (2017): Conservation Genetics, Special issue: Conservation Genetics of Bee Pollinators, Volume 18 (3)

3. Fair and equitable sharing of benefit will be compromised

As mentioned above, the inclusion of DSI in the scope of the Nagoya Protocol will lead to legal and regulatory uncertainty and will impede scientific research as it attaches indefinite access and benefit sharing obligations to the use of such information. Thus, we doubt whether fair sharing mechanisms between provider and user can be developed at all.

Regardless as to how the system will be organized in detail – a complete control of Access and Benefit Sharing related to DSI is virtually impossible, as monitoring and checking compliance would be extremely burdensome or even impossible to achieve for providers or users. It will cause enormous transaction costs which will negatively affect research in all countries including provider countries, whose scientists will suffer foremost and most severely.

International research cooperation involving DSI will face many more difficulties than already existing. The willingness to conduct joint (including biodiversity related) research projects most probably will decline – entailing a decrease in training and capacity building for scientists from the developing countries, thus compromising Article 12 (Research and Training) of the CBD.

Whilst the resultant efforts and costs will be huge for the international research community, the financial benefit for the provider countries might be unexpectedly minor: If research is delayed or prevented, there won't be any benefit to share at all. If there is a benefit to share, it might have to be divided between many different provider countries which gave access to the (physical) genetic resources the DSI involved in the study were related to.
But due to the nature of bioinformatics, in most of the cases it will not be possible to judge what a single sequence has actually contributed to the results. Thus, it will be quite unfeasible to negotiate a commonly accepted fair distribution key.

Importantly, the Protocol already allows for provider countries in their PIC or MATs to limit DNA sequencing and information distribution on a case-by-case basis where relevant and necessary. We would urge the committee to encourage provider countries to use the mechanism that are already available rather than to use a wide, blunt mechanism like the complete and full inclusion of DSI.

4. The inclusion of DSI will assault the special considerations of the Nagoya Protocol (Art. 8)

According to Nagoya Protocol Art. 8a, all parties shall "create conditions to promote and encourage research which contributes to the conservation and sustainable use of biological diversity, particularly in developing countries, including through simplified measures on access for non-commercial research purposes (…)"
Although most access to genetic resources for research occurs without commercial intention[6], provider countries have generally been unwilling or legally unable (because of their legislation) to provide simplified access to genetic resources for non-commercial research. Given the different character of DSI, the preparedness to provide simplified procedures for non-commercial research using DSI will be even smaller. Thus, we suspect that non-commercial research will have to undergo the same efforts commercial research must. Given the fact that non-commercial funding of research projects is generally more limited than commercial funding, the inclusion of DSI will result in the relative discrimination of non-commercial funding against commercial funding - just the opposite of what was intended by Nagoya Protocol Art 8a.

[6] Buck, M., Hamilton, C. (2011): The nagoya protocol on access to genetic resources and the fair and equitable sharing of benefits arising from their utilization to the convention on biological diversity. - Review of European Community and International Environmental Law, Volume 20 (1): 47-61. DOI: 10.1111/j.1467-9388.2011.00703.x

Art. 8b of the Nagoya Protocol pays special attention to *"cases of present or imminent emergencies that threaten or damage human, animal or plant health, as determined nationally or internationally".* However, the inclusion of DSI in the scope of the Nagoya Protocol may instead challenge national and international biosecurity and public, animal and plant health issues even more than the already existing legislations and regulations concerning genetic resources themselves[7] [8]. The use of DSI allows for swift compilation, comparison and reanalysis of genetic information from a variety of sources, across multiple databases and gene sequences which are linked to the mentioned emergencies. Thus, open access to DSI is a prerequisite for rapid tackling disease outbreaks and the emergence of drug resistance through the development of effective, reliable prophylactic measures (e.g. vaccines), diagnostics and treatment (e.g. pharmaceuticals) for pathogens, pests and invasive species.
Emergencies require instantaneous action and appropriate tools DSI can provide. Any abdication of this tool will compromise the ethical imperative of immediate action using the best instruments available.

Recommendations of the German Life Sciences Association (VBIO e. V.) concerning the inclusion of DSI under the scope of the Nagoya Protocol:

- With respect to the remarks above, DSI should not fall within the scope of the Nagoya Protocol at all. If a provider country decides to restrict the use of DSI which is linked to a genetic resource accessed on its territory, it already can do so by applying national laws. By this, the provider country has to balance the possible benefits of this policy with the threads mentioned under (3) and (4).
- To identify possible solutions for covering the ethical considerations related to the use of DSI in research -- especially in the field of Synthetic Biology -- further stakeholder engagement should be put forward.
- It might appear that other regulatory tools, such as e.g. Intellectual Property Rights will serve better to comprehensively cover ethical issues.
- Any mechanism employed to ensure benefit sharing should be proportionate and seek to avoid limiting the capacity of researchers to collaborate and share the materials and outputs of their research, such as DSI.

For queries and further information, we are happy to provide additional input from our Association or its scientific experts.

Contact:

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[7] E. g. WHO EXECUTIVE BOARD (2016): Review of the Pandemic Influenza Preparedness Framework (Report by the Director-General to WHO EXECUTIVE BOARD EB140/16 (140th session, 29 December2016 Provisional agenda item 7). - http://apps.who.int/gb/ebwha/pdf_files/EB140/B140_16-en.pdf

[8] WHO Secretariat (2016): IMPLEMENTATION OF THE NAGOYA PROTOCOL AND PATHOGEN SHARING: PUBLIC HEALTH IMPLICATIONS. Advance copy. 30pp - http://www.who.int/influenza/pip/2016-review/NagoyaStudyAdvanceCopy_full.pdf