Subject - **Pressing need for mRNA vaccines' urgent carcinogenicity and genotoxicity studies**

To whom it may concern,

Abstract
We doctors and scientists from different countries and different backgrounds, signatories of this letter, are making a call to anyone in a position to request, require, mandate, decide or conduct carcinogenicity studies that have become essential and urgent. We offer this letter to health agencies, judges, lawyers, laboratories, universities or anyone in a position to make such independent studies happen.

We understand this letter may be used in a court of law and are willing to provide explanations upon request.

We are guided by scientific findings and the desire for safety of our fellow citizens. Such studies would enlighten the medical and scientific community about the risks and their amplitude, and would guide us to organize eventual early screening, mitigation actions and possible anticipation of dangers and their solutions.

In this letter we explain why such SAFETY studies are needed, given ongoing massive vaccination campaigns. We also explain why new findings increase cause for concern. As such, it has become an absolute urgent necessity to conduct such studies.

We have found cause for concern and require these studies to anticipate how large and how serious the risks may be, since no scientist or wise person can claim to know the future. Thus we need this information to prepare eventual mitigation scenarios and minimize impacts on peoples' health; to provide screening and protection to the vaccinated.

Given the stakes, such studies are a very small price to pay, to mitigate eventual consequences.

1) Safety studies including carcinogenicity studies need to be conducted for a new intervention, using 2 new technologies (Lipidic Nano Particles and mRNA), for a new virus, on an immensely large population in a repetitive manner

In relation to the Covid pandemic, new vaccines have been created in a record time. Two such vaccines rely on a novel mRNA technology used for the first time in the area of vaccination. They are NEW technologies directed against a NEW virus. Urgency and high emotional stress has led to the application of NEW processes and NEW rules particularly in safety assessment. Rapid deployment has led to creation of NEW setups in manufacturing, conservation and delivery.

Such multiple NOVELTIES have led Pfizer and Moderna (manufacturers) to require and be granted immunity against legal action related to safety issues that may arise later. Urgency and high emotional stress may explain why governments have accepted these changes in usual safety processes and granted such immunity to manufacturers. We question strenuously the manufacturers' insistence on being given medicolegal immunity from any and all proceedings that might arise from the delivery of such injections of unknown consequences in the next months or years.

Medical agencies [1] [2], have relied on a document from the World Health Organization dated 2005 stating « Carcinogenicity studies are not required for vaccine antigens. However, they may be **required for particular vaccine components such as novel adjuvants and additives** »[3] This WHO document refers to vaccination technologies that had been evaluated multiple times and

existed before novel mRNA vaccination and new associated unknown risks..

That same 2005 document defines adjuvants as being « Substances that are intended to enhance relevant immune response and subsequent clinical efficacy of the vaccine. »

Pfizer's website explains mRNA vaccination as follows « mRNA, delivered to your body's cells by lipid nanoparticles, instructs the cells to generate the spike protein found on the surface of the novel coronavirus that initiates infection.1,2 Instructing cells to generate the spike protein spurs an immune response, including generation of antibodies specific to the SARS-CoV-2 spike protein »[4]

For example the European Medicines Agency (EMA) recommendation states [5]

"The objective of this guideline is to define the conditions under which carcinogenicity studies, should be conducted to avoid the unnecessary use of animals in testing..."

"The fundamental considerations in assessing the need for carcinogenicity studies are the maximum duration of patient treatment and any perceived **cause for concern arising from other investigations**. **Other factors may also be considered such as the intended patient population**, prior assessment of carcinogenic potential, **the extent of systemic exposure**, the (dis)similarity to endogenous substances, the appropriate study design, or the timing of study performance relative to clinical development."

"Certain classes of compounds may not be used continuously over a minimum of 6 months but may **be expected to be used repeatedly in an intermittent manner**." In this regard, the hypothesis emitted by the vaccine developers suggesting that there will be a need for 'booster' vaccinations on a yearly or even more frequent basis argues that carcinogenicity concerns, based on repeated exposure, are valid.

"For pharmaceuticals developed to treat certain serious diseases, carcinogenicity testing need not be conducted before market approval although **these studies should be conducted post-approval**. This speeds the availability of pharmaceuticals for **life-threatening or severely debilitating diseases**, especially where no satisfactory alternative therapy exists." Carcinogenicity studies must be conducted as an urgent matter. After carcinogenicity studies are properly conducted with the right animal models, with a reassuring outcome, post approval phase 4 may begin. It must also be considered that COVID 19 does not meet the definition of " life-threatening or severely debilitating diseases" [6] [7] [8]for vast portions of the population such as those already immune, young people, and middle age healthy people. As a sidenote, although agencies are hesitant, multiple(?) re-purposed drug therapy is being used de facto worldwide with documented success on vulnerable population.

Contrary to what was announced initially, biodistribution reports indicate **systemic exposure** as they show distribution in liver, adrenal glands, spleen, blood, bone marrow and ovaries for Pfizer[9] as well as liver, adrenal glands, heart, eye, kidneys, testis, blood, bone marrow and brain for Moderna[10] More elements have come to light confirming such wide distribution of nanoparticles into the body, their persistence with embedded mRNA and subsequent production of spike protein both from possibly leaked Japanese authorities and studies. [11]

This was foreseeable, as the new lipid nanoparticles (LNP) were designed initially in medicine for mass bio-distribution. They are used in medicine to deliver/transport drugs to distant sites in the body for cancer treatment, as well as other treatments. Their core function is to reach distant tissues. As expected, Nanoparticles, embedded RNA, and subsequent production of spike protein spreads into multiple organs. These biodistribution findings differ from what has been known about

previous vaccines and substances staying at the injection site. This alone is sufficient to require at the very least immediate extensive carcinogencity studies.

Booster, repeated vaccination is being suggested after 6 months or a year repeatedly for populationsSuch repetition further strengthens the absolute necessity of such studies. [12]

Use of recent technology and new mechanisms require more testing to better apprehend associated risks, and if necessary, to put in place actions to mitigate them.

Precautionary principle requires that such studies be fully performed, preferably by independent groups, so that results can be trusted by scientists and the public.

If full safety is confirmed, this would be reassuring for all, and if there are risks identified, particularly from the carcinogenicity studies, it would allow for early screening and treating those at risk.

In addition to necessity for public safety at a moderately low cost, out of precaution, such studies done concurrently to ongoing EUA would also provide additional scientific benefits related to future use of such technologies indicating which risks need further exploration.

These arguments in themselves justify for an urgent need to mandate [EMA] to perform or at least require such studies, particularly the carcinogenicity one.

As covid vaccination is progressing, in many countries, deployment of such vaccinations have been explained by urgency due to an ongoing epidemic. In that context, safety assessment procedures were altered with the promise that full extended safety studies would be carried out concurrently instead of linearly. EUA's were granted and people have been vaccinated, trusting that all safety procedures have been completed or are in progress.

Nothing can justify betraying such trust and **skipping or delaying further safety studies altogether** to avoid possible injurious outcome or responsibility allocation. Yet, medicines agencies have not required genotoxicity and carcinogenicity studies.[13] [14]

<u>Several findings raise cause for concern and indicate multiple emerging mechanisms by which these mRNA vaccines could cause, induce or lead to an increased risk of cancer.</u>

As mentioned above, need for carcinogenicity studies has become all more pressing given that **systemic exposure** has been shown from pharmacokinetics and biodistribution studies. LNP with embedded mRNA reach multiple organs such as [liver, adrenal glands, spleen, ovaries, heart, eye, kidneys, testis, bone marrow and brain].

Scientific findings beg the implementation of safety studies to help reassure the public and scientific community and to potentially organize mitigation actions in such massive vaccination, based on the findings of such studies.

1. That **spike protein has been shown to interact with p53 protein** which has been shown to be involved in **multiple cancers possibly up to 50% of cancers**.[15] [16]Much knowledge is still needed as to understanding how much spike protein is produced, for how long, and in which organs ? Differences in interactions need to be understood when the spike protein is present alone, as with mRNA, compared to when attached to a virus, as happens naturally or with adenovirus vaccines. Spike protein has been seen to freely circulate in the blood stream possibly up to 29 days after injection [17]

2. A preprint from the Radboud University Netherlands, the Hannover medical school Germany and the University of Bonn Germany finds that the Pfizer vaccine may result in **changes to innate immunity**.[18] **Innate immunity plays an important role in cancers** [19 20]
3. **The spike protein is a known toxin.** [21] [22 23 24]And in relation to this, we know that following injection, the vehicles carrying the mRNA that encode for the spike protein are heterodispersed throughout the body as shown by the above-mentioned biodistribution studies shared by manufacturers with European and Japanese authorities. This leads to the production of **free spike protein at levels that would never be seen in patients with natural SARS CoV-2 infection**. Moreover, the toxic effects of the spike protein can now be produced, by passing the blood-brain barrier of the mRNA-containing nanolipid structures within the brain. However, in opposition to the claims made by the manufacturers, the spike protein encoded by vaccinal mRNA does not remain bound to the cell membranes, and can be found freely in the bloodstream, which exposes the vaccinated person to an even more protracted attack from spike protein. **It has also been shown that nanoparticles containing mRNA seem to reach multiple organs, including the liver, testis, ovaries and bone marrow, possibly leading to spike protein production and causing cancers**[25] [26].
4. Human and viral reverse transcriptases are families of enzymes that allow the creation of segments of DNA from RNA so the DNA can be encoded within the human genome. We have evidence that RNA coding for SARS-CoV-2 major proteins could be reverse transcribed into human DNA in several different ways, some of which are known and some are to be discovered.[27] [28] [29] [30]Given this evidence, that reverse transcription happens, and given the immense size of the healthy young population being vaccinated in a short period of time, downstream changes to the Human genome could have unwanted effects[31] including oncogenic ones.[32] We also note that if the DNA encoding for spike protein is taken up into the Human genome, and is incorporated downstream of an active promotor region, production of this toxic protein could increase the risk for several disorders, ranging from cancer to cardiovascular disease.

1) **New LNP**, 2) **New mRNA** vaccination, 3) **Systemic exposure**, 4) **Immense intended population**, 5) **Repeated use.** A**ny single one** of these elements would alone suffice to **require immediate safety carcinogenicity** studies. 6) Spike protein **interacting with P53**, 7) **Suspicion** of altering **innate immunity**, 8) **Free spike toxin** reaching **organs** 9) **Risks of integration.** Each would be sufficient **cause for concern for an immediate carcinogenicity study**. **Taken together**, they lead **us signatories of this letter to make this urgent, essential call for these safety studies** to be conducted IMMEDIATELY, THOROUGHLY and INDEPENDENTLY to handle an unprecedented situation.

For all above-mentioned reasons, we call upon anyone who has the authority to request, mandate, order or undertake all steps to make sure all such studies, using the same substances as for humans, reproducing methods and frequency of administration, and ensuring these studies are performed as per best practices as indicated in attached guidelines[33] preferably by independent bodies. Such studies should be conducted with the same substances injected in humans and reproduce booster doses on two appropriate animal models having similar ACE2 receptors as humans, such as ferrets, minks or golden hamsters. We understand that only humans can give safety on humans, but until that happens during phase 4 with proper scrutiny, carcinogenicity studies give us indications on risk amplitude and where to pay attention for early screening, mitigation and treatment actions. We also request that raw data be made available and public in a continuous transparent manner.

This is all the more essential ethically [34] [35] [36] [37], as vaccination is being carried out on a very large scale, in healthy populations at negligible risk of severe disease or in covid recovered patients who were explicitly excluded from Moderna and Pfizer [38] [39] trials and have no benefit. They could face

months or years of deadly or severely debilitating adverse events in addition to already known short-term inflammatory, circulatory, nervous, and allergic serious adverse events.

With much needed humility, and safety studies, we could collectively spare innumerable lives, and the health of many more individuals.

1 https://www.ema.europa.eu/en/documents/scientific-guideline/ich-s-1-need-carcinogenicity-studies-pharmaceuticals-step-5_en.pdf
Eurpoean Medicines Agency EMA July 1996
2 Public Assessment Report Authorisation for Temporary Supply COVID-19 mRNA Vaccine BNT162b2 (BNT162b2 RNA)
Medicines & Healthcare Regulatory Agency (MHRA)
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/944544/COVID-19_mRNA_Vaccine_BNT162b2__UKPAR___PFIZER_BIONTECH__15Dec2020.pdf
3 WHO guidelines on nonclinical evaluation of vaccines Annex 1
WHO Technical Report Series, No. 927, 2005
https://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/ANNEX%201Nonclinical.P31-63.pdf?ua=1

4 https://www.pfizer.com/news/hot-topics/the_facts_about_pfizer_and_biontech_s_covid_19_vaccine
Accessed 14/06/2021
5 https://www.ema.europa.eu/en/documents/scientific-guideline/ich-s-1-need-carcinogenicity-studies-pharmaceuticals-step-5_en.pdf
Eurpoean Medicines Agency EMA July 1996
6 https://www.lawinsider.com/dictionary/life-threatening-condition
Accessed June 22nd 2021
7 https://medical-dictionary.thefreedictionary.com/severely+debilitating+illness
Accessed June 22nd 2021
8 https://www.lawinsider.com/dictionary/debilitating-medical-condition
Accessed June 22nd 2021
9 https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf
10 https://www.ema.europa.eu/en/documents/assessment-report/covid-19-vaccine-moderna-epar-public-assessment-report_en.pdf
11 Ogata AF et al.
Circulating SARS-CoV-2 Vaccine Antigen Detected in the Plasma of mRNA-1273 Vaccine Recipients
Clinical Infectious Diseases May 2021
https://doi.org/10.1093/cid/ciab465
12 https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-initiate-study-part-broad-development
13 EMA
https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf
14 EU Risk management plan Moderna
EU Risk Management Plan for COVID-19 mRNA vaccine
covid-19-vaccine-moderna-epar-risk-management-plan_en.pdf (europa.eu)
15 Nishant Singh et al.
S2 subunit of SARS-nCoV-2 interacts with tumor suppressor protein p53 and BRCA: an in silico study
Translational Oncology Elsevier October 2020
https://doi.org/10.1016/j.tranon.2020.100814
16 Liz J. Hernández Borrero, Wafik S. El-Deiry,
Tumor suppressor p53: Biology, signaling pathways, and therapeutic targeting,
Biochimica et Biophysica Acta (BBA) - Reviews on Cancer, 2021
https://doi.org/10.1016/j.bbcan.2021.188556
17 Ogata AF et al.
Circulating SARS-CoV-2 Vaccine Antigen Detected in the Plasma of mRNA-1273 Vaccine Recipients
Clinical Infectious Diseases May 2021
https://doi.org/10.1093/cid/ciab465
18 Konstantin Fohse F et al.
The BNT162b2 mRNA vaccine against SARS-CoV-2 reprograms both adaptive and innate immune responses
medRxiv May 2021
doi: https://doi.org/10.1101/2021.05.03.21256520
19 Jinushi M
OncoImmunology 2012
The role of innate immune signals in antitumor immunity
https://doi.org/10.4161/onci.1.2.18495
20 Corrales L et al.
Innate immune signaling and regulation in cancer immunotherapy
immunotherapy. Cell 2017
https://doi.org/10.1038/cr.2016.149

21 Tanmay S et al.
Is SARS-CoV-2 Spike glycoprotein impairing macrophage function via α7-nicotinic acetylcholine receptors?
Food and Chemical Toxicology 2021
https://doi.org/10.1016/j.fct.2021.112184
22 Lei Y et al.
SARS-CoV-2 Spike Protein Impairs Endothelial Function via Downregulation of ACE 2
Circulation research March 2021
https://doi.org/10.1161/CIRCRESAHA.121.318902
23 Buzhdygan TP et al.
The SARS-CoV-2 spike protein alters barrier function in 2D static and 3D microfluidic in-vitro models of the human blood–brain barrier
Neurobiology of disease December 2020
https://doi.org/10.1016/j.nbd.2020.105131
24 Rhea EM et al.
The S1 protein of SARS-CoV-2 crosses the blood–brain barrier in mice
Nature Neuroscience December 2020
https://doi.org/10.1038/s41593-020-00771-8
25 Singh N et al
Inflammation and cancer
Ann Afr Med [serial online] 2019
DOI: 10.4103/aam.aam_56_18
26 Coussens, L., Werb, Z.
Inflammation and cancer.
Nature 420, 860–867 (2002).
https://doi.org/10.1038/nature01322
27 Geuking M B et al
Recombination of Retrotransposon and Exogenous RNA Virus Results in Nonretroviral cDNA Integration
Science Jan 2009
DOI: 10.1126/science.1167375
28 Belyi V et al.
Unexpected inheritance: multiple integrations of ancient bornavirus and ebolavirus/marburgvirus sequences in vertebrate genomes
PLOS PATHOG July 2010
DOI: 10.1371/journal.ppat.1001030
29 Chandramouly G et al.
Polθ reverse transcribes RNA andpromotes RNA-templated DNA repair
Science Advances Jun 2021:
DOI: 10.1126/sciadv.abf1771
30 Zhang L et al.
SARS-CoV-2 RNA reverse-transcribed and integrated into the human genome
BioRxiv December 2020
https://doi.org/10.1101/2020.12.12.422516
31 Ming-Hsiang L M
Somatic APP gene recombination in Alzheimer's disease and normal neurons
Nature 2018
https://doi.org/10.1038/s41586-018-0718-6
32 Sigal A et al.
Oncogenic Mutations of the p53 Tumor Suppressor: The Demons of the Guardian of the Genome
Cancer research December 2000
https://cancerres.aacrjournals.org/content/60/24/6788
33 OECD GUIDELINE FOR THE TESTING OF CHEMICALS: CARCINOGENICITY STUDIES
June 25 2018
https://www.oecd-ilibrary.org/docserver/9789264071186-en.pdf?expires=1623621149&id=id&accname=guest&checksum=4924859A984B8D84730C17CA9C4979D7
34 https://www.ama-assn.org/delivering-care/ethics/code-medical-ethics-overview
Accessed 22/06/2021
35 https://www.wma.net/policies-post/wma-international-code-of-medical-ethics/
Accessed 22/06/2021
36 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3399321/
Accessed 22/06/2021
37 https://www.conseil-national.medecin.fr/sites/default/files/external-package/edition/168yke7/code_de_deontologie_version_anglaise.pdf
Accessed 22/06/2021

38 https://www.clinicaltrials.gov/ct2/show/NCT04470427
Clinicaltrials.gov June 2021
39 https://clinicaltrials.gov/ct2/show/NCT04368728?term=Pfizer&cond=covid&age=2&phase=12&draw=2&rank=3
Clinicaltrials.gov June 2021