Briefing Note for IARC Scientific and Governing Council members

Prepared by the IARC Director

January 2018

I. Background

Since the evaluation of glyphosate by the IARC Monographs Program in March 2015, the Agency has been subject to unprecedented, coordinated efforts to undermine the evaluation, the program and the organization. These efforts have deliberately and repeatedly misrepresented the Agency's work. The attacks have largely originated from the agro-chemical industry and associated media outlets. They have taken place in the context of major financial interests relating to: a) the relicensing of glyphosate by the European Commission; b) hundreds of litigation cases in the USA brought by cancer patients against Monsanto, claiming that their malignancies were caused by glyphosate use; c) and the decision by the Californian Environmental Protection Agency to label glyphosate as a carcinogen.

In response to the misrepresentations, the Agency has sought to provide a clear account of its actions, including keeping its governing bodies informed of developments. Many of the relevant documents have been posted in the public domain on the IARC Governance website[1] and on dedicated glyphosate webpages[2]. IARC scientists have responded to industry-funded critiques appearing in scientific journals by published letters to journal editors. Given its limited capacity, IARC has not tried to develop an extensive media campaign to present its position, or to counter all industry-sponsored attacks in the media. However, in selected and important cases, IARC has addressed the false claims in the media[2].

II. Follow-up from IARC Scientific and Governing Councils 2017

The above areas were discussed at the Scientific and Governing Council meetings in 2017. The Director has briefed the Chairs and Vice-Chairs of the respective Councils over the last year during regular teleconferences. The Agency remains confident in the Monograph evaluation of glyphosate. These various discussions have also covered ongoing work to clarify the relationship between the IARC Monographs program on cancer hazards and the

[1] http://governance.iarc.fr/ENG/infocouncils.php

[2] http://www.iarc.fr/en/media-centre/iarcnews/2016/glyphosate_IARC2016.php

WHO risk assessment exercises, particularly when the same agents are subject to evaluation. In May 2017 in resolution GC/59/R2, the Governing Council expressed *"support to the Director in his effort to work with the senior leadership at WHO to further enhance cooperation and encourages the development of a standard operating procedure to optimize communication in relation to cancer hazard identification and risk assessment"*.

The IARC Director met with the new WHO Director-General, Dr Tedros Ghebreyesus, in August 2017 to discuss cooperation between IARC and WHO, including the relationship between the respective hazard identification and risk assessment exercises, in line with the WHA request (Resolution WHA 70.12) to the Director-General *"to enhance the coordination between IARC and other parts of WHO on assessments of hazards and risks, and on the communication of those assessments"*. The IARC Director and WHO Director-General agreed on the steps, actions and responsibilities to be taken prior to the IARC Governing Council and World Health Assembly in May 2018 and these are the subject of ongoing work. The topic is planned as an agenda item at the IARC Governing Council meeting.

In response to a request from the Chairs and Vice-Chairs of the Councils, the Director has prepared the current briefing note to provide clarity with respect to some repeated misrepresentations and criticisms of the Monograph evaluations. It is hoped this will be a useful reference for Council members when similar accusations about the Monographs program are repeated.

III. IARC response to criticisms of the Monographs and the glyphosate evaluation

A number of quite specific and other more general criticisms have been aimed repeatedly at the glyphosate evaluation and the wider Monographs program. Many criticisms in the media originate from one Reuters journalist; another source is a March 2015 article that Forbes[3] since removed from their website, ending their relationship with the author amid revelations in the New York Times that the article was ghostwritten by Monsanto. A

[3] https://www.nytimes.com/2017/08/01/business/monsantos-sway-over-research-is-seen-in-disclosed-emails.html

number of these criticisms were included subsequently in two letters to the IARC Director from the US House of Representatives Committee on Science, Space and Technology[4].

IARC did not edit parts of the glyphosate Monograph to achieve a particular outcome

- The Reuters journalist[5] obtained a draft of parts of the glyphosate Monograph from Monsanto and compared the draft with the final, published version of the Monograph. On this basis the journalist claimed IARC had selectively edited the text to favor an evaluation of glyphosate as *"probably carcinogenic to humans"*. The majority of the highlighted differences were related to a review article co-authored by a Monsanto scientist, which has been the subject of investigative reporting concerning "ghost-writing". The Agency rejected the false claims published by Reuters[6].
- The Working Group considered that information contained in the review article was insufficient to allow independent scientific evaluation. As a result, the draft text was revised by the Working Group; the text in the published Monograph is its consensus opinion.
- For all Monograph evaluations, the drafts prepared over the months prior to a meeting form the basis of open and detailed scientific debate during the eight-day evaluation meeting in Lyon and are modified by the Working Group as a result.
- Changes made to the draft documents are the result of deliberation between Working Group members and are not attributable to any particular scientist.
- IARC staff (secretariat to the meeting) do not draft or revise the Monograph text, which is the preserve of Working Group members.

Data from the Agricultural Health Study (AHS) were not deliberately excluded from the Monograph

- One suggestion made in media reports is that results from the AHS were withheld from the IARC Monograph evaluation and that recent results would have led to a different evaluation[7] . Monsanto lawyers obtained draft scientific manuscripts of the AHS as a result

[4] http://governance.iarc.fr/ENG/Docs/CLSBiggs-IARC_01112017.pdf; http://governance.iarc.fr/ENG/Docs/CPWild-LSmith&ABiggs.pdf; http://governance.iarc.fr/ENG/Docs/SST_IARC12082017.pdf http://governance.iarc.fr/ENG/Docs/CPWild_Smith_Biggs_Lucas_20180111.pdf
[5] https://www.reuters.com/investigates/special-report/who-iarc-glyphosate/
[6] http://www.iarc.fr/en/media-centre/iarcnews/pdf/IARC_Response_Reuters_October2017.pdf
[7] https://www.reuters.com/investigates/special-report/glyphosate-cancer-data/

of calling the Principal Investigator of the AHS, Dr Aaron Blair to testify in litigation hearings in the US. IARC rejected the claims publicly[8].

- The AHS is a prospective study that has been ongoing since the 1990s and publications date back more than 20 years, with incremental updates published periodically. For the 2015 classification of glyphosate, several peer-reviewed publications from the AHS were available and included in the evaluation. At the time of the Monograph evaluation the latest AHS publication did not report an association between non-Hodgkin lymphoma and glyphosate. However, this null finding did not outweigh the positive associations found in other epidemiological studies.
- The most recent analysis from the AHS only became available in 2017 - 30 months after the Monograph evaluation - and was consistent with the prior results included in the Monograph, except that new data on increased leukemia risk with glyphosate exposure were not available to the Working Group in 2015.
- Because the Monograph classification reflects the consensus view of the Working Group, based on a systematic review of all publicly available studies, it is inappropriate to speculate about how new data from one study might change that expert opinion.
- The lengthy court testimony given by Dr. Blair does not support any change in the classification of glyphosate consequent to the latest AHS publication. To the contrary, when asked, *"Has anything you've been shown by Monsanto's lawyers in the 3 hours and 40 minutes that he questioned you changed the opinions that you had at the IARC meeting about glyphosate and non-Hodgkin lymphoma?"*, Dr. Blair answered, *"No"*.[9]

IARC Monograph evaluations are transparent and open to scrutiny

- The suggestion has been made that IARC's Monograph evaluations lack transparency[10] because the draft documents are not made available and changes to drafts are not ascribed to specific Working Group members.
- Draft and deliberative materials are not made public, in order to protect the Working Group scientists from interference by vested interests. The position of IARC and WHO

[8] http://governance.iarc.fr/ENG/Docs/IARC_responds_to_Reuters_15_June_2017.pdf

[9] Videotaped deposition of Aaron Earl Blair, PhD. March 20, 2017. MDL No. 2741, Case No. 16-md-0271-VC. United States District Court, Northern District of California.

[10] https://www.reuters.com/article/us-health-cancer-iarc-exclusive/exclusive-who-cancer-agency-asked-experts-to-withhold-weedkiller-documents-idUSKCN12P2FW

concerning the public release of deliberative documents, or records of deliberative scientific discussions, is consistent with standard practice in scientific committees.

- For example, the Monographs approach is in line with the US National Research Council; reports from the US National Research Council routinely indicate that, *"the review comments and draft manuscript remain confidential to protect the integrity of the deliberative process."* [11]
- IARC's practices are also consistent with the Joint Meeting on Pesticide Residues (JMPR) (jointly administered by the FAO and WHO), which evaluated glyphosate in 2016, in particular with regard to the confidentiality of draft and deliberative documents, the determination of conclusions and decisions by consensus from all participants, and the adoption of the final report by the *"entire Meeting"*.[12]
- It is noteworthy that Monograph meetings are open to scientific stakeholders in order to balance participation *"from constituencies with differing perspectives"*[13]. All participants have full access to the draft documents and discussions. For example, the meeting on glyphosate included an Observer from Monsanto and a Representative from the US Environmental Protection Agency (EPA). The Monsanto Observer was quoted in the media as saying: *"The meeting was held in accordance with IARC procedures. Dr Kurt Straif, the director of the Monographs, has an intimate knowledge of the rules in force and insisted that they be respected."*[14]

IARC has a strong rationale for inclusion of only publicly available studies in Monograph evaluations

- The Monographs have been accused of selective use of scientific studies ("cherry-picking"[15]) because Working Groups consider only reports available in the public domain, identified and documented through the systematic assembly and review of all publicly available and pertinent studies, as specified in the Monographs Preamble. This practice is criticized because it excludes studies conducted by industry when these are publicly unavailable.

---

[11] Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde (2011) https://www.ncbi.nlm.nih.gov/books/NBK208227/; Review of EPA's Integrated Risk Information System (IRIS) Process (2014) https://www.ncbi.nlm.nih.gov/books/NBK230074/

[12] http://www.who.int/foodsafety/publications/jmpr_guidance_document_1.pdf?ua=1

[13] http://monographs.iarc.fr/ENG/Preamble/currenta5participants0706.php

[14] http://www.lemonde.fr/planete/article/2017/10/18/glyphosate-monsanto-tente-une-derniere-man-uvre-pour-sauver-le-roundup_5202606_3244.html

[15] https://www.nature.com/news/widely-used-herbicide-linked-to-cancer-1.17181

- The Monographs do not exclude research conducted by industry *per se*. Where industry-conducted studies are published in scientific journals they are considered, if available in sufficient detail to allow independent scientific review. Under the same conditions, the Monographs also take account of industry-conducted research in summary form or if placed in the public domain by national regulatory agencies.
- The need for industry-conducted studies to be publicly accessible is in line with the existing (e.g. European Medicines Agency) or developing (e.g. European Food Standards Agency) policies of other international agencies.
- Consistent with the above principles and as required by its Preamble, the glyphosate Monograph did not consider any unpublished information on the AHS (see above). However, as already mentioned, the Working Group did include published reports from the AHS.
- IARC follows its current practice in order to enable others to scrutinize the basis of its decisions rather than relying on appeals to authority or trust. This transparency is fundamental to the scientific process.

Monograph Working Group members who evaluated glyphosate were free from conflict of interests

- Another suggestion is that the Working Group evaluation of glyphosate was unduly influenced by Dr Christopher Portier[16], who was an Invited Specialist at the meeting[17]. It is suggested that Dr Portier had contractual commitments to US law firms involved in glyphosate litigation at the time of the Monograph meeting.
- IARC is not aware of any contractual relationship existing between Dr. Portier and litigation lawyers relating to glyphosate at the time of the Monograph meeting in March 2015, when glyphosate was evaluated. However, IARC did take account of other real or apparent conflict of interests declared by Dr. Portier, specifically his part-time role with the Environmental Defense Fund. On this basis, IARC invited his participation in the meeting as an Invited Specialist and his declared conflict of interest was made public on the IARC Monograph website two months in advance of the glyphosate evaluation.
- Dr. Portier had full access to draft documents and discussions during the meeting, and was recognized to speak at the meeting. However, as an Invited Specialist, Dr. Portier was not

[16] https://www.reuters.com/investigates/special-report/health-who-iarc/
[17] http://governance.iarc.fr/ENG/Docs/SST_IARC12082017.pdf

a member of the Working Group that was responsible for the critical reviews and evaluations developed during the meeting, including the work performed in sub-groups assessing the epidemiology, animal bioassays or other relevant mechanistic data.

- None of the 16 Working Group members - or any other meeting participant (including the Observer from Monsanto, other Observers, and the US EPA Representative) - signaled any attempt at undue influence by Dr. Portier.
- A related suggestion has been that Dr Portier influenced the original decision to evaluate glyphosate[18] through chairing the April 2014 meeting of the "Advisory Group to Recommend Priorities for IARC Monographs during 2015-2019". However, this Advisory Group comprised 21 members from 13 countries and recommended over 80 different agents for IARC to consider for evaluation over the five-year period mentioned, one of which was glyphosate. The IARC Secretariat took the decision on the five agents to be reviewed at the Monograph meeting in March 2015.

IARC evaluates only agents that have some evidence of carcinogenicity

- Some critics say the Monographs program finds "everything causes cancer"[19] because of nearly 1000 agents evaluated only one has been categorized in Group 4, "probably not carcinogenic to humans".
- The criticism is misleading because the Monographs do not select at random the agents evaluated for carcinogenicity. Instead, in the interest of efficiency and according to the Preamble to the Monographs, "Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity."
- IARC puts out a public call for agents to be reviewed and establishes the "Advisory Group to Recommend Priorities for IARC Monographs" to propose priorities for evaluation of agents based on the criteria mentioned above.
- Despite this careful selection of agents, in reality around half (502 of 1003) of the Monograph evaluations resulted in agents being classified in Group 3 ("not classifiable as to its carcinogenicity to humans"); just 12% of all agents evaluated (120 of 1003) are Group 1 ("carcinogenic to humans") and a further 38% (380 agents) fall into Group 2B

[18] https://www.reuters.com/investigates/special-report/health-who-iarc/
[19] Ibid.

("possibly carcinogenic to humans") or 2A ("probably carcinogenic to humans"). This is far from the finding everything is carcinogenic.

Monograph evaluations take account of "real-world" exposures by evaluation of epidemiological studies

- A charge levelled at the Monographs is that evaluations are divorced from the "real world" i.e. are made without taking account of realistic human exposures.
- However, epidemiological studies are a central part of Monograph evaluations and, by definition deal with people exposed in daily life, including at work. The studies frequently consider the gradient of risk observed with different levels of exposure. One part of the Monograph evaluation is specifically dedicated to describing the circumstances under which human exposure occurs and at what levels.
- In addition, when considering scientific evidence of carcinogenicity including biological mechanisms, the Working Groups place special emphasis on whether the observations are relevant to humans.
- In light of occurring ("real world") human exposures, Working Groups synthesize evidence in humans, animals and other model systems in reaching overall conclusions.

The Monographs program re-evaluates an agent when a substantial additional body of scientific evidence becomes available

- As a science-driven process, the Monographs program has a responsibility to re-evaluate an agent when a significant additional body of evidence becomes available. However, this has led to updates being labelled as a "retraction"[20] if the classification changes, as when coffee was re-evaluated in 2016. The implication that if an evaluation changes then all evaluations are open to doubt not only misrepresents the Monographs but misunderstands science. Science is not static; evidence accumulates and understanding evolves, thus enabling updated evaluations.
- In practice, by far the most frequent change in classification after re-evaluation is that the agent goes into a higher group (e.g. Group 2A to 1). The fact that most re-classifications

[20] https://oversight.house.gov/wp-content/uploads/2016/09/2016-09-26-JEC-to-Collins-NIH-IARC-Funding-due-10-10.pdf

move into a higher group is an objective indicator that the Monographs do not overstate the strength of available evidence but are in fact conservative in nature.

- A scientifically updated classification is not, therefore, equivalent to a retraction. Rather, re-evaluation is the sign of a strong, science-driven program responding to scientific progress.

The Monograph evaluations group agents according to the strength of evidence of carcinogenicity, not their potency

- The Monograph evaluation results in a classification based on the strength of evidence that an agent causes cancer or not. In other words, it is a measure of how confident the Working Group is that this agent causes cancer in humans.
- The Monograph evaluations do include consideration of the level of exposure (dose) associated with the risk of developing cancer (response) and strong dose-response relationships corroborate the confidence that a particular agent is a cause of the cancers observed. However, this potency of the agent i.e. how many cancers it causes at certain exposure levels, is not the basis of classification.
- Consequently agents with different potencies can be placed in the same classification group. For example, various forms of tobacco, plutonium, diesel engine emissions, hepatitis viruses and processed meat all have sufficiently strong evidence to classify them in Group 1. The distinction between strength of evidence and magnitude of effect is highlighted in media communications and on the Monographs website in order to make this distinction clear[21].

IARC Monographs identify carcinogenic hazards and do not include a risk assessment

- The IARC Monographs identify carcinogenic hazards i.e. those agents having the potential to cause cancer under some circumstances. This has led some to downplay the relevance of hazard identification[22] and even to suggest the exercise is without value.

[21] http://monographs.iarc.fr/ENG/News/Q&A_ENG.pdf

[22] See internet archive (https://web.archive.org/web/20170220012554/https://www.forbes.com/sites/henrymiller/2015/03/20/march-madness-from-the-united-nations/#6d6581212e93, best viewed with Microsoft Edge and Safari browsers), as cited in https://www.nytimes.com/2017/08/01/business/monsantos-sway-over-research-is-seen-in-disclosed-emails.html.

- The IARC Monographs program is explicit about the difference between hazard identification and risk assessment on its website[23].
- In fact, identifying carcinogenic hazards is a crucially important and necessary first step in risk assessment and management; it should be a "red flag" to those charged with protecting public health.
- Revealing that an exposure is a threat (or hazard with a Group 1, 2A or 2B classification) should trigger either immediate remedial action (e.g. bans, as with asbestos or access to artificial tanning salons for young people, or labelling of carcinogenic hazards) or further evaluation of the scale of the risk (risk assessment) in order to set the levels of exposure a particular society is willing to accept (e.g. control measures in occupational settings; acceptable levels of airborne pollutants, or food contamination by pesticides, etc.).
- In contrast to hazard identification, the specific exercise of risk assessment typically involves extrapolation beyond the observed data, employs a variety of statistical models and is based on anticipated levels of exposure and background cancer incidence rates that are often specific to a population or region.
- Following risk assessment, decisions on managing risk encompass social, economic and political considerations. For the above reasons, IARC defers risk assessment and risk management to national and international bodies, restricting itself to provision of hazard identification as a scientific foundation to those subsequent steps.
- This area of debate brings into sharp relief the different and often imprecise ways the word risk is used and understood. A quantitative examination of the elevated risk associated with a given exposure is an integral part of hazard identification, as a support to causal inference. But this differs from the statistical exercises of quantitative risk assessment described above.
- There is clear value in IARC and WHO liaising closely in future exercises of hazard identification and risk assessment and as mentioned in Section II of this document, discussion is in progress.

IARC evaluations make use of the latest scientific data and methodologies

- The IARC Monographs pioneered and continue to be a leader worldwide in objective, systematic cancer hazard evaluations.

[23] http://monographs.iarc.fr/ENG/News/Q&A_ENG.pdf

- Authoritative reviews, including by the National Research Council of the US (NRC, 2011, 2014, 2018)[24], have heralded IARC's review and evaluation methodology, citing it as exemplary and recommending it as one potential model for adoption by US national risk assessment programs.
- Additionally, the IARC Monographs data integration process has been adapted to other systematic review methodologies[25].
- The Monographs Program has received funding from the NCI/NIH USA for over thirty years. The most recent proposal received a score close to the best possible in the current NIH evaluation system. This rating therefore reflects a very high scientific esteem for the programme on the side of the independent reviewers.
- The Monographs program undergoes scientific review by a Review Panel (composed of IARC Scientific Council members and external experts), most recently (in 2014) receiving the highest possible rankings for performance (Outstanding) and fit with the Agency's mission (Perfect).
- A subsequent IARC Monographs Advisory Group concurred with the Scientific Review Panel in supporting the current system of selection and use of experts for the cancer hazard evaluations, accompanied by strict management of conflict of interests. The Advisory Group also encouraged the Program to disseminate the findings of the evaluations as broadly as possible to the scientific and technical community, policymakers and the general public.
- In consideration of this valuable peer review input, and also taking into account positive peer review by the US NCI, the Programme remains committed to conducting reviews that are scientifically rigorous, respected, and free of conflict of interests.

---

[24] Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde (2011). https://www.ncbi.nlm.nih.gov/books/NBK208227/; Review of EPA's Integrated Risk Information System (IRIS) Process (2014). https://www.ncbi.nlm.nih.gov/books/NBK230074/; Using 21st Century Science to Improve Risk-Related Evaluations (2018). https://www.ncbi.nlm.nih.gov/books/NBK424983/

[25] Environ Health Perspect. 2014 Oct; 122(10): 1007–1014. doi: 10.1289/ehp.1307175; Environ Health Perspect. 2014 Jul;122(7):711-8. doi: 10.1289/ehp.1307972