

Draft Statement

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FORMALIN BANNING IN EUROPE IN 2016

ESP Molecular Pathology Pre-analytical Tissue Condition WG and UEMS Section of Pathology*

Executive summary

With the reclassification of formalin in terms of carcinogenicity from category 2/3 to category 1B/2 the EU intends to ban the use of formalin in 2016. In the considerations leading to these decisions and in the underpinning data the medical use of formalin is almost completely ignored. In close interaction with the National Societies of Pathology of the European countries, the European Society of Pathology (ESP) and the UEMS Section of Pathology have deemed it necessary to take position in this issue which can be summarized as follows:

1. Formalin is an indispensable component of what in pathology is called 'pre-analytical' sample treatment. Any cell or tissue specimen taken out of a patient needs to be preserved in order to allow further processing. Tissue preservation is universally attained by infiltration of the specimen with formalin, which is one of the great examples of standardization in pathology.
2. In spite of intensive research, a suitable alternative for formalin has not been identified. Without formalin fixation pathologists will no longer be able to diagnose disease. In the EU this would imply that each year for more than 50 million patients, half of which cancer patients for whom therapy choice depends on the diagnosis of the pathologist, diagnoses will no longer be made. Against this background the ESP and the UEMS Section of Pathology cannot accept the ban on the use of formalin.
3. In view of the reclassification of formalin, the pathology research community will continue its search for alternatives for formalin, with characteristics in the process of fixation equal to or even better without the health hazards ascribed to formalin.
4. Banning formalin is a simplistic approach, given what has been outlined in points 1 and 2. It is not only the categorization of formalin that needs to be taken into consideration but, more importantly, the level of exposure at the working place. The workers should and are willing to accept the risk for the benefit of their patients, but at the same time have a legitimate request to healthcare administrators to provide the most safe conditions possible, including necessary investments. In pathology departments those workers regularly exposed to samples fixed in formalin will be offered working conditions in which the measured formalin levels are below those regarded as hazardous

The pathology community proposes a scientifically valid position on this issue to be communicated to EU officials before the new rule becomes in force. A strongly defended position is that it is not the use of formalin as such that is a risk but the proper working conditions.. The risk of health problems caused by exposure can be reduced by working conditions where the exposure of workers in pathology is limited to a minimum. The technology and procedures to provide such conditions exist.

1. At present there are no alternative fixatives validated to serve as formalin replacement: formalin fixation is the basic requirement of standardized tissue preservation for clinical diagnostic procedures. Any use of new fixatives will have the consequence to introduce new products into the clinical practice, with new characteristics requiring new extensive validation procedures in histological, immunohistochemical (IHC) and molecular analyses and thus the reproducibility of today's diagnostic procedures would be heavily endangered. Most of the prognostic and predictive biomarkers are performed at the IHC level and this will continue in the future with the requirements for new immune-therapy approaches. Standard fixation conditions are absolutely important to obtain reproducible and communicable results. Comparable treatment protocols will be extremely difficult. The rate of histological misdiagnoses followed by wrong treatment decisions will increase dramatically, which will have massive consequences on patient-centered care. At present there is no alternative available to formalin, which has been sufficiently validated. New validation processes will require many years and it may take a decade or more to reach complex new compromises for a new standardization. Reproducibility is the first requirement for any clinical procedure. The damage for the health system and for patients will be incommensurably bigger than the advantages to ban formaldehyde from the environment. The responsibility for this development will be on the side of the EU commission.

2. Formalin is used in hospital pathology labs with specific precautions that can be further improved: The new European rules are based on the principle to protect the environment and the people getting in touch with aldehydes for professional reasons. In pathology departments, formalin fumes are avoided by the use of chemical hoods, and this can be easily extended to other hospital areas such as the surgical theatre, where formalin is managed. New proposals like vacuum treatment of the surgical specimens, which avoids the use of formalin in the surgical theatre and has already been adopted by some of the major hospitals of Europe, could be a very efficient solution. This will even improve the pre-analytical conditions of tissues with the consequence of better molecular diagnoses. In the medical ambulatories where small biopsies are taken, the formalin problem is solved by using prefilled tubes to lower the exposition to minimal levels.

3. Formalin is a cheap procedure of fixation, any other solution will increase the costs: Formalin is inexpensive especially in comparison with the new commercial alternatives for new formalin-free fixatives. Any alternative to formalin, even in case it is properly validated, will increase the costs of histopathological diagnosis. Health care is not prepared to cover increased spending. Other costs, related to all the changes in procedures connected with the use of new fixatives, and especially the long time to reach again a common standardization throughout Europe have also to be considered.

4- Formalin and the risk of cancer: The risk to develop cancer by the exposure to formalin is reported in literature with controversial results. This does not lower the attention that should be given to this environmental risk especially on the professional level. The exposure to formaldehyde in the past was lower in the health system than in other industrial applications. It always has to be considered that this risk can be individually highly increased by specific genetic patterns or by concomitant other types of exposure with a multiplicative effect. Therefore, any risk should be effectively considered as real. The technical precautions to avoid exposure must be maintained at the maximum level.

Conclusions: The use of formalin and its banning cannot be considered in the European health system without generating major harm to the quality of diagnosis for patients. This will especially compromise the new type of molecular diagnosis that is mostly based on IHC and is strictly related to the new biological type of therapies. Discussion on this problem is extremely urgent because of the

short time before specific rules are applied in Europe, which brings about different approaches in the different European countries, generating confusion in the health institutions. At the same time the risk of exposure under current working conditions should be carefully taken into consideration: any technical improvement to reduce it to safe borders should be adopted. It is necessary to consider special exemptions for formalin use in the European health systems, demanding at the same time that health control authorities check transport, personnel exposure and discharge.