

FORMALIN BANNING IN EUROPE IN 2016

*ESP Molecular Pathology – Pre-analytical Tissue Condition WG**

Executive summary

With the reclassification of formalin in terms of carcinogenicity from category 2/3 to category 18/2 EU intends to ban the use of formalin in 2016. In the considerations that have led to these decisions and in the data underpinning them 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 has deemed it necessary to take position in this issue. This document elaborates the arguments underpinning the ESP position. ESP position can be summarized as follows:

1. Even though not well known to the public at large and, in view of the scientific literature on health hazards of formalin, even to specialists in the field of chemical carcinogenesis, 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. The universal use of formalin is one of the great examples of standardization in pathology.
2. In spite of fairly intensive research, a suitable alternative for formalin has not been identified. This document provides references to substantiate this conclusion. 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 be no longer made. Against this background ESP does not 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, of which the characteristics in the process of fixation are equal to or even better than those of but without the health hazards ascribed to formalin.
4. Banning formalin is a simplistic approach, given what has been outlined in points 1 and 2. In reality, 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. 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. This is attained by:
 - working under a safety hood
 - under adequate ventilation
 - for limited periods of time
 - with regular measurement of real time formalin levels.

- Formalin is in the process of being formally banned in the European countries in 2016. This is a consequence of the EC Regulation n.605/2014 of 05.06.2014 that modifies the EC Regulation n.1272/2008. Formaldehyde has been moved as carcinogen from category 2/3 (carcinogenicity is suspected but not proved) reported in the Reg. 2008 to category 1B/2 (in which carcinogenicity is presumed). Also mutagenicity was included in category 2 (suspected mutagen). This could have different types of consequences from a practical point of view in the use of formalin in Europe, even in its use as tissue fixative for human tissues in diagnostics.

The general opinion is that the pathology community should come up with 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; the issue is what the proper working conditions. The risk of health problems caused by exposure can be limited by creating working conditions in which the exposure of workers in pathology is limited to an acceptable minimum. The technology and procedures to provide such conditions exist.

The European Society of Pathology Advisory Board in the meeting held on 5th of September 2015 made the proposal for an ESP position document on this issue.

This document is not meant to be a technical report but an alarm to be disseminated to European policy makers.

We as pathologists have the responsibility to present our concerns and considerations to European legislators and to health policy makers:

1. There are no alternative fixatives currently validated to serve as formalin replacement: formalin fixation is the basic requirement of standardized tissue preservation for clinical diagnostic procedures. Formalin is quite deleterious to preserve macromolecules, and new fixatives could increase their availability for molecular analyses. On the other hand, we have seen that there is room to improve nucleic acid preservation also with formalin, as proposed by Bussolati et al with the process of cold fixation (1). 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. That means 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. New fixatives are going to take to the use of new antibodies that should be adapted and standardized for several different fixatives. 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. There is no alternative currently available to formalin, which has been sufficiently validated. The validation process will require many years. It will take then a decade or more to reach very 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 also to other hospital areas such as the surgical theatre, where formalin is managed. The protection level can be further improved with more efficient technologies of transport, storage, use and discharge of formalin. New proposals like vacuum treatment of the surgical specimens (2), 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 increase 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 the use of prefilled tubes that are already used to lower the exposition to minimal levels.

Today there are efficient technical procedures to eliminate formalin residues already active in any European hospital and the discharge precautions can be further improved.

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 also have to be taken into consideration, they are 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.

4- Formalin and the risk of cancer:

The risk to develop cancer by the exposure to formalin is reported in literature with controversial results (3). This does not lower the attention that should be given to this environmental risk especially on the professional level. The exposure to formaldehyde even in the past was evidently lower in the health system than in other industrial applications, but 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. For this reason, 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.

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