

Letter to the editor

Formaldehyde: From Interstellar Space to the Pathology Laboratory

Dear editor,

In the 1970s, first as a professor of Pathology at the Faculty of Medicine of the National University of La Plata, Argentina, and later during my 6 years of residency at the pathology laboratory of the Javier Muniz Hospital in Buenos Aires, and even to this day, the pungent odor of formaldehyde remains in my olfactory memory, irritating all mucous membranes. Nowadays, things are different, with air purification systems, exhaust fans, laminar flows, etc., that all laboratories have or should have (since formaldehyde is extremely toxic), allowing us to coexist with it to a certain degree of safety. Fixation is a critical step in histopathology[1]. Technology has provided pathologists with a wide range of tools to protect us. However, formaldehyde remains the fixative par excellence, meeting almost all the criteria of a good fixative.

In the process of preparing biological specimens, it is crucial to adhere to certain criteria for effective fixation. These guidelines ensure the preservation and observation of cellular structures. The key principles include:

Timely Action: Act swiftly to kill and fix cells before the onset of agonic or post-mortem phenomena such as autolysis and disintegration.

Penetration Power: Possess a high level of penetration power to guarantee proper fixation, even in the deeper layers of the specimen.

Preservation of Structural Details: Strive to conserve the structural details observed in vivo during the fixation process.

Facilitation of Observation: Allow or facilitate the use of necessary procedures for subsequent observation, such as sectioning and staining.

Prevention of Element Loss: Prevent the disappearance of soluble elements during or after the fixation process[2,3].

Avoidance of Artificial Structures: Refrain from inducing or preventing the formation of artificial structures during fixation.

Tissue Integrity: Maintain the integrity of tissues by avoiding excessive retraction, brittleness, or friability.

Adhering to these principles ensures not only the success of the fixation process but also the accurate representation of cellular structures for further scientific observation and analysis. Most of these criteria are fulfilled by formalin at its appropriate concentration for tissue fixation. Fixation with formalin is universally accepted as an ideal fixative, and its effect is considered a "gentle" fixation.

Formaldehyde was discovered by August Wilhelm von Hofmann in 1863, and its introduction as a fixative was in 1893, marking an important step in tissue preservation [4]. It can be said to have existed since ancient times, with the molecular alteration induced by formaldehyde, involving the formation of cross-links between proteins or between proteins and nucleic acids, through methylene bridges.

Tissue fixed with 10% formaldehyde, embedded in paraffin, and stained with H-E, allows for diagnosis in the majority of cases, and although it may require additional techniques later, it is important to first visualize it with H-E to then analyze the differential diagnosis and, when necessary, perform more specific techniques [5]. In summary, formaldehyde is a widely used fixative due to its excellent tissue preservation properties. It acts as a preservative, causing minimal tissue shrinkage, and is compatible with most histological techniques and stains[6]. Compared to other fixatives, protocols for histopathological analysis that use formalin as a fixative gain in practicality, cost-effectiveness, and ease of procurement. The use of formalin as a fixative is practical, cost-effective, and highly efficient, making it a preferred choice in histopathological analyses[7,8].

But our ally, formaldehyde, has a long history before it reaches the pathologist's table.

What is the origin of formaldehyde? How long has it been in the universe?

Scientific discoveries suggest that formaldehyde was one of the first substances in the universe. Interstellar formaldehyde was first discovered in 1969 by L. Snyder et al. [9], who, using the National Radio Astronomy Observatory, detected it in comets and asteroids during the formation of our solar system.

Over time, the substance underwent chemical reactions to form complex organic molecules. These comets and asteroids could have collided with our planet during its early years, leaving behind their precious cargo rich in carbon and water, essential for the evolution of life [10]. In our laboratory, we have the golden fixative, formaldehyde, which has been in the universe for 13.7 billion years, and today we have it on our table as a fundamental element to practice our profession as pathologists.

Curious, isn't it?

References

- [1] Abler TA, Green J, Shotkin S, Whiting JD, Hughes RO, Calvert RC, Johnson FB, Fox CH. Variation in Formaldehyde Fixation in Routine Histopathology Laboratories. *Journal of Histotechnology* 1983;6(4):181-184.
- [2] Culling CFA, Reid PE, Sinnott NM. The Effect of Various Fixatives and Trypsin Digestion Upon the Staining of Routine Paraffin-Embedded Sections by the Peroxidase-Antiperoxidase and Immunofluorescent Technique. *Journal of Histotechnology* 1980;3(1):10-19.
- [3] Rezaian M. Modification of Fixation Process in Avian Histologic Sections. *Journal of Histotechnology* 2006; 29(2):123-127.
- [4] Binawara B, Rajnee CS, Mathur K, Sharma H, Goyal K. Acute effect of formalin on pulmonary function tests in medical students. *Pak J Physiol.* 2010;6:8-10.
- [5] Romano LA, Pedrosa VF. Re-claiming H&E: back to the future. *Postgraduate Medical Journal*, p. postgradmedj 2019;136955-2.
- [6] Armed Forces Institute of Pathology (U.S.). Manual of histologic staining methods of the Armed Forces Institute of Pathology. In: Luna LG, ed. 3rd ed. New York: Blakiston Division, McGraw-Hill, 1968.
- [7] Benerini Gatta L, Cadei M, Balzarini P, Castriciano S, Paroni R, Verzeletti A, Cortellini V, De Ferrari F, Grigolato P. Application of alternative fixatives to formalin in diagnostic pathology. *Eur J Histochem.* 2012;56(2):e12.
- [8] Obi EN, Tellock DA, Thomas GJ, Veenstra TD. Biomarker Analysis of Formalin-Fixed Paraffin-Embedded Clinical Tissues Using Proteomics. *Biomolecules.* 2023;13(1):96.
- [9] Snyder LE, Buhl D, Zuckerman B, Palmer P. *Phys. Rev. Lett.* 1969;22:679.
- [10] Chen L, Woon DE. A theoretical investigation of the plausibility of reactions between ammonia and carbonyl species (formaldehyde, acetaldehyde, and acetone) in interstellar ice analogs at ultracold temperatures. *J Phys Chem A.* 2011;May 26;115(20):5166-83.