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## **Carcinogenic effects of antibiotic residues in meat: Clinical and statistical perspective**

**Amine Berghiche**

Institute of Agronomy and Veterinary Science, University Mohamed Cherif Messaâdia, Souk Ahras, Algeria & Laboratory of Science and Technique of Living, Institute of Agronomic and Veterinarian Sciences, University Mohamed Cherif Messaâdia, Souk Ahras, Algeria

Corresponding author email: [amine\\_berghiche@yahoo.com](mailto:amine_berghiche@yahoo.com) / [a.berghiche@univ-soukahras.dz](mailto:a.berghiche@univ-soukahras.dz)

**Ibtissem Labiad**

Institute of Agronomy and Veterinary Science, University Mohamed Cherif Messaâdia, Souk Ahras, Algeria & Laboratory of Science and Technique of Living, Institute of Agronomic and Veterinarian Sciences, University Mohamed Cherif Messaâdia, Souk Ahras, Algeria

**Bouzid Riad**

Laboratory of agriculture and ecosystems fonctionnary, University Chadli Bend Djedid El Tarf, Algeria & University Chadli Bend Djedid El Tarf, Algeria

**Abstract**--Through this research note we focused on the subject of the link between the use of antibiotics and its residues in the human and animal body and the appearance of tumors. A clinical and statistical perspective is conducted in our note, through examples of literature that have discussed this topic in which the impact of some antibiotics is determined theoretically and the interdiction of some molecules is made in some countries, but in fact and statistically the application of adequate etiological study "cohort" in order to correlate the causes and effects is failed because the conditions of feasibility is incomplete or poorly defined. In vitro studies, modeling and docking are required to confirm or affirm the hypotheses about the subject.

**Keywords**---antibiotics residues, clinical perspective, statistical perspective, impact, Cohorte.

## Introduction

Since the discovery of antibiotics, human beings have lived in the era of antibiotic therapy, where these molecules ensure the treatment of humans and animals from the past to the present. [1, 2] Besides the phenomenon of resistance, which is a warning on the horizon, the appearance of cancer due to antibiotics is still a subject that researchers have not yet discovered or avoided, although the high number of cases of tumors requires the etiological study of all kinds of chronic synthetic chemical exposure in humans and animals in order to evaluate the impact of treatments on health and to assess the impact of therapies that may be a negative arsenal in the coming years. [3, 4, 5]

Carcinogenesis results primarily from interactions of the carcinogen with cellular DNA; the changes induced can be fixed and then become definitive and heritable, which means that carcinogens act as mutagens. [6, 7, 8] Some antibiotics have well-determined carcinogenic properties. These molecules residues have a carcinogenic effect on the long term, following the regular consumption of food containing these compounds. [9, 10, 11, 12] For example, nitrofurans, nitroimidazols are banned for use in livestock; and malachite green in fish. [13, 14, 15] Nitrofurans are antibiotics that are used in human medicine for a short time in patients, but these molecules are widely recognized as genotoxic carcinogens. [15, 16]

## Clinical Plan

Clinically, most chemical carcinogens, apart from alkylating and acylating agents, require prior activation; this may be simple (transformation of a procarcinogen into a carcinogen in a single step) or complex (several steps required for activation) and the activation sequence may lead to a final inactivation step. [17, 18] Many carcinogens are metabolized by cytochrome P-450-dependent oxygenases located in the microsomal fraction of the endoplasmic reticulum and in the nucleus. This enzymatic activity is dependent on many environmental and genetic factors that influence the ability to activate procarcinogens, a genetic influence on the activity of an enzyme such as CP-450 and contact with enzyme inducers (e.g. phenobarbital) that can enhance the activity of microsomal enzymes such as CP-450. [19, 20, 21, 22, 23]

Many other factors are likely to interfere in the metabolism of a procarcinogen and to modify the carcinogenic effect of a substance: the hormonal state, the nutritional state for example the CP-450 dependent activation system is not the only one to come into play in the activation of procarcinogens: the systems of peroxidation, reduction, conjugation to glutathione are also involved. [19, 22, 23] Animal experiments demonstrated that their prolonged use could lead to changes in genetic material and to the development of tumors. [24]

The potential mutagenic and carcinogenic potential of these compounds is due to the nitro-reduction of the drug, leading to the formation of electrophilic metabolites and their binding to DNA, they are rapidly metabolized in the body and their in vivo stability does not exceed a few hours; Thus, most of the nitrofurans residues in foodstuffs are bound to proteins, mainly covalently, and their carcinogenicity is thus annihilated. [24, 25, 26]

The binding of genotoxic chemical compounds to proteins is a non-adverse biological effect that operates as a defense mechanism effectively abolishing the genotoxic potential of electrophilic compounds and thus preventing electrophilic attack of DNA; These compounds formed with amino acids in proteins are extremely stable (there is no repair mechanism unlike what happens with DNA compounds) and are eliminated almost unchanged in the urine following the normal protein cycle. But the complexes "nitrofuran residue - protein" are then suspected to have an allergic effect. [27, 28]

### **Statistical Plan**

In 1948, Framingham conducted the first study to evaluate the impact of myocardial ischemia on mortality and recurrence, this study was the first in the history of evaluation called "Cohort". [29] The cohort study has an important methodological advantage (prospective). It allows a high degree of precision in measuring exposure to the factor(s) and its consequences, and in terms of causality the chronology is respected. [29]

It is most often carried out following an initial case-control survey, the results of which can be refined, most often prospective (the frequency of the disease is measured in one or two groups) and more rarely retrospective (useful in the case of collective food poisoning or occupational diseases), but they are made for frequent affections then in the case of the residues of antibiotics and its harmful effects this condition is missing [30, 31].

The evidence of correlation between the occurrence of cancer and exposure to certain antibiotics and their residues, even if they are officially recognized as carcinogenic, is still lacking in the conditions of application of statistical etiological tests of the "Cohort" type, due to the existence of several parameters of variability that affect the results [31, 32].

### **Conclusion**

Although the existence of a direct relationship between the use of antibiotics and cancer is difficult to determine and even to predict by statistical studies such as the cohort study, it does not prevent us from seeking confirmation of this question by other types of in vitro studies or modelling and docking for example.

### **Disclosures**

**Ethics Committee Approval:** Ethics committee approval was not requested for this study.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

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