Natamycin$^{(R)}$

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Natamycin (pimaricin), a polyene (tetraene) macrolide compound is produced by the actinomycete *Streptomyces natalensis*. In crystalline form it is a colorless, tasteless, odorless and stable compound, which is nearly insoluble in water (as little as 50 mg/l) and most organic solvents. Good solvents for natamycin are strongly polar organic solvents (methylpyrrolidone, for instance). In common with other polyenes, the "dissolved" molecules form suspensions of micelles. Stability is notably influenced by pH, light, heavy metals and oxidants (Raab, 1972).

Natamycin is very stable between pH 4.5 and 9. It is characterized by an intense ultraviolet absorption spectrum, which serves as the basis of a non-specific spectrophotometric analysis (Raab, 1972).

A specific analysis with a minimal detection limit of 25–30 nanograms has been developed by using HPLC linked to the spectrophotometer. Of corresponding sensitivity is the specific bioassay. Natamycin is exceedingly active against nearly all fungi, MIC's usually being below 15 µg/ml. It fails to act against organisms without sterols, in particular ergosterol, in their cell membranes. Natamycin forms a complex with ergosterol, with the result that the permeability of the cell membrane changes, inorganic ions and metabolites leak away and the cell ultimately dies.

The action may thus be said to be fungicidal. The tendency to complex formation with cholesterol is extremely limited so that cell membranes in higher animals will not be affected.

In the case of fungi, natamycin is, as a rule, highly active against young, dividing cells. Since spores are not killed, the compound cannot be regarded as sporicidal. As distinct from many other types of compounds, no cases of in vivo resistance to polyenes are known. Less sensitive strains of e.g. *Candida albicans* may sometimes be obtained by repeated transfers onto polyene-containing media but especially in the case of natamycin this is of rare occurrence. Such more tolerant strains show different morphological and physiological properties, such as a lower ergosterol content in the cell membrane, a slower growth in clusters, no pseudomycelium formation and total loss of virulence. On that basis, Hamilton-Miller (1974) has remarked that "from a clinical point of view the problem of polyene resistance is nonexistent". In none of the tests carried out according to the transfer procedure mentioned above, with different cultures of fungi isolated from cheese warehouses, was it possible to obtain less sensitive strains (De Boer and Stolk-Horsthuis, 1977).

Natamycin is non-toxic (LD_{50} in rats = 2.5–4.5 g/kg), non-mutagenic, non-carcinogenic, non-teratogenic and non-allergenic. No abnormalities were seen in rats and their litters after oral administration of 1000 µg/ml of natamycin per day over a period of 2 years.

The acceptable daily intake (ADI) has been established at 0.30 mg/kg by WHO and FAO. The average consumer of cheese and sausage ingests daily about 0.002 mg/kg of natamycin (= < 1% ADI).

Medical applications of natamycin are confined to the treatment of vaginal and other skin mycoses and pulmonary aspergillosis.

In the food sector natamycin is applied especially to counteract fungal infections that may occur during the ripening process of cheeses and sausages. Used in this way, it also prevents the formation of mycotoxins.

Because of its poor solubility, natamycin scarcely, if at all, penetrates into the product, in hard cheeses < 1 mm and in rindless French cheeses about 2–4 mm. Upon ripening, natamycin slowly disappears, which in the case of cheese often necessitates another treatment.

The application of natamycin to already mouldy products serves no useful purpose. Natamycin is accepted as a preservative in Argentina, Chile and South Africa for use in fruit drinks, wines, etc., where it serves to prevent secondary fermentations. It also appears to give entire satisfaction in storing silage such as grass and cabbage leaves where it prevents aerobic degradation by fungi. Here, however, the cost price becomes a decisive factor.

This is also the case with the use of natamycin as an antifungal agent on fruit, seed potatoes and daffodil bulbs, although results are usually satisfactory.

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Wood deterioration by microorganisms and its prevention

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Deterioration by microorganisms of wood in service may lead to enormous economic losses. So it will be obvious that measures to avoid premature deterioration are taken. Microorganisms inhabiting wood may be divided into organisms decomposing the wood cell walls and those not able to do so.

To the first group belong the fungi causing brown, white and soft rot. Brown-rot fungi (e.g. *Serpula lacrimans*) and white-rot fungi (e.g. *Coriolus versicolor*) belong to the *Basidiomycetes* and soft-rot fungi either to the Ascomycetes (e.g. *Chaetomium globosum*) or to the Fungi Imperfecti (e.g. *Trichoderma viride*). Brown-rot fungi decompose mainly cellulose, white-rot fungi lignin and cellulose and soft-rot fungi cellulose and some lignin.

To the second group belong blue-stain fungi, mold fungi and some species of bacteria. Blue-stain fungi have dark-brown hyphae and may penetrate deeply into the wood. Macroscopically, the wood gradually turns greyish-blue. Mold fungi cause a discoloration of the wood surface mainly due to the production of masses of coloured spores. Blue-stain and mold fungi belong to the Ascomycetes or to the Fungi Imperfecti. In comparison with rot fungi the damage done by blue-stain and mold fungi is very small.

Bacteria (e.g. *Bacillus polymixa*) may develop in ponded wood and then cause a large increase in permeability of the sapwood. Especially the pit membranes of the wood are deteriorated.

The main factors influencing the development of fungi in wood are moisture content and temperature. Moreover, the natural durability of the wood species involved has a dominating influence. Fungi will not develop in wood when the moisture content is lower than 20% (calculated on oven-dry weight). The moisture content may also be too high for fungal development. Wood saturated with water under anaerobic conditions will not be attacked. Wood saturated with water containing sufficient air, e.g. wood in cooling towers, may be deteriorated by soft-rot fungi.

Wood-inhabiting fungi may grow in a temperature range of about +3 to about +40 °C. The optimum temperature is generally about +25 °C. Some fungi, however, prefer a somewhat lower or a

[1] Retired.