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Divisione di Chimica dell'Ambiente
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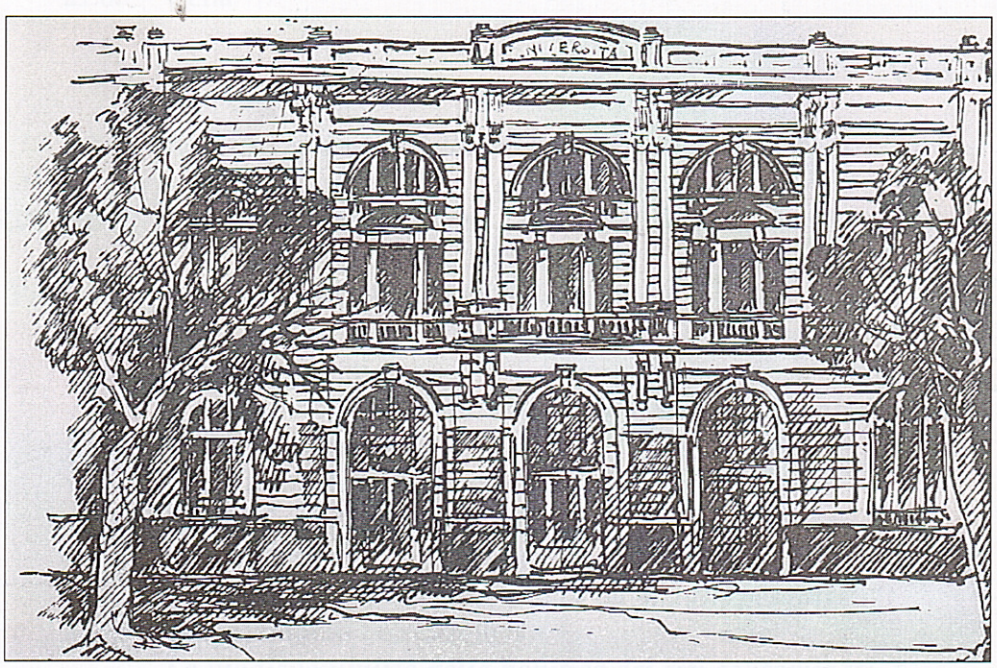
III Conferenza Organizzativa

Inquinamento da metalli pesanti: la biodisponibilità



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MOLECULAR MECHANISMS OF NICKEL CARCINOGENESIS: NICKEL BINDING TO HISTONE H4 AND CAP43 PROTEIN

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The carcinogenicity of nickel compounds has been confirmed and corroborated by numerous epidemiological studies in humans and carcinogenesis bioassays in animals [1].

Although the mechanisms of nickel-induced carcinogenesis are not well-known, they are believed to involve genetic and epigenetic routes. Nickel compounds influence carcinogenesis by interfering with a variety of cellular targets. We found that nickel is a potent inhibitor *in vivo* of histone H4 acetylation, in both yeast and mammalian cells [2]. It has preference to specific lysine residues in the N-terminal-$S_1GRGK_5GGK_8GLGK_{12}GGAK_{16}RH_{18}RKVL_{22}$ histone H4, in which the sites of acetylation are clustered.

The metal ion is able to bind histidine H_{18} in the N-terminal which protrude out from the nucleosome [3].

We also found that an excellent tumour marker recently discovered and specifically induced by nickel, Cap43 protein, has a new mono-histidinic motif consisting of ten amino acids TRSRSHTSEG repeated three times in the C-terminus which is able to bind several metal ions in a cooperative way [4,5].

References

[1] IARC, Lyon, France, *Monographs on the evaluation of carcinogenic risks to humans*. 1990; Vol. 49.

[2] Broday L, Peng W, Kuo MH, Salnikow K, Zoroddu M, Costa M. *Nickel compounds are novel inhibitors of histone H4 acetylation*. Cancer Res. 2000; 60(2):238-4.

[3] Zoroddu MA, Peana M, Kowalik-Jankowska T, Kozlowski H, Costa M. *The binding of Ni(II) and Cu(II) with the N-terminal tail of the histone H4.* J. Chem. Soc., Dalton Trans., 2002, 458–465

[4] Zoroddu MA, Kowalik-Jankowska T, Kozlowski H, Salnikow K, Costa M. *Ni(II) and Cu(II) binding with a 14-aminoacid sequence of Cap43 protein, TRSRSHTSEGTRSR*. J Inorg Biochem. 2001;84(1-2):47-54.

[5] Zoroddu MA, Peana M, Kowalik-Jankowska T, Kozlowski H, Costa M. *Nickel(II) binding to Cap43 protein fragments*. J Inorg Biochem. 2004; 98(6): 931-9.

Molecular Mechanisms of Nickel Carcinogenesis:
Nickel Binding to Histone H4 and Cap43 Protein

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