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POLYHEXAMETHYLENE BIGUANIDE BEARS SIMILAR MODE OF ACTION TO ANTI-DIABETES BIGUANIDES

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Abstract: PolyHexaMethylene Biguanide, PHMB (CAS n° 32289-58-0, previously 91403-50-8) derives from an antiseptic chemical group. This active ingredient is used in a wide range of applications, amongst which: hard surface disinfectant, water treatment (sanitizer, particularly in swimming pools), product preservative agent, bacteriostatic in industrial processes and water systems, personal care products preservative, etc. Based upon a carcinogenesis study in the rat (OECD 453), PHMB/G from Paréva is being proposed for classification as suspected carcinogen in rats by the competent authorities in France and Europe, even though PHMB is neither genotoxic nor mutagenic and is not classified by IARC, while the mechanism triggering tumours is unknown. Considering the close structural relationship of PHMB with Biguanides its effects on glucose metabolism and consecutively on energy production in the cells were evaluated. Since the overall conclusion of in vivo studies pointed at the liver as the main target organ for PHMB, the experiments were performed on HepG2 cells (from a human hepatocellular carcinoma), to assess its properties on cellular handling of glucose for ATP production and consecutive vascular endothelial growth factor (VEGF) production. PHMB inhibits the phosphorylation of 2-DG and Glucose, so that G-6-P levels are reduced and glucose cannot be used further. As a confirmation of this inhibition of phosphorylation, ATP formation is inhibited by up to 77%, leading possibly to cell death. PHMB inhibits also the production of vascular endothelial growth factor (VEGF) in similar range of PHMB concentrations (0.5 - 5 µg/ml). The inhibition of glucose phosphorylation for ATP production and consequently the inhibition of Vascular Endothelial Growth Factor production by PHMB confirms the similarity of the mode of action with Biguanides, used as anti-diabetes. This inhibition might prevent endothelial cells proliferation and angiogenesis, so that it is unlikely that PHMB will promote either liver vascular endothelial cells or Hep-G2 cells in vitro or hepatocytes growth in vivo or tumours. Recent advances in these molecular mode of action and their consequences on tumour prevention or cell growth will be presented and discussed.