Paris, 03/10/2022

Five protein complexes constitute the central core of the mitochondrial respiratory chain, (MRC) the third of them, complex III being the target of Metyltetraprole (MTP). This MRC is highly conserved through evolution and the action of MRC inhibitors, such as MTP, are therefore hardly specific to a given species.

MRC complex III is well known for its propension to produce free radical species, initially superoxides, upon disturbance of its activity. In excess, superoxides represent a major threat for genetic material of the cells. Beside nuclear DNA, mitochondrial DNA (mtDNA) due to its intramitochondrial location will be particularly at risk. Noticeably, with their peculiar transmission law, mtDNA mutations will be readily transmitted to descendants. As surprising as it is, such mutations particularly at risk when using MRC inhibitors such as MTP have not and are still not sought when studying genotoxicity.

To date, independent experimental works on the toxicity of MTP are extremely scarce. The desire, no doubt dictated by their low cost, to substitute "in silico" studies based on computerized metabolic charts to these experimental studies, now represents a real danger. We have experienced “in silico” studies in the case of SDHIs, and found these totally incapable of representing the complexity of biological situations: tissue specific and varying contents of metabolites, epigenetics modifications, DNA damage, for each drug such as MTP degradation or concentration in the organism, etc.

Unfortunately, the experimental studies required by regulations to test the toxicity of mitotoxic substances like MTP, also present major problems. To cite only two of them: the studies on human cells in culture are supposedly carried out in the presence of glucose although the presence of glucose is known to mask any toxicity of a mitotoxic product; As noted above, the genotoxicity studies which exclude the study of the mitochondrial genes are dangerously incomplete.

Finally, we know that more than 40% of the approximately 600 pesticides present in the environment are likely to interfere with the use of oxygen by the mitochondria. The simultaneous presence of these mitotoxic substances represents a source of uncontrollable and inescapable cocktail effects which given their impressive possible number are hardly seriously studyable.

For all these reasons, it would be irresponsible to put MTP on the market.

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