Classification of cytochrome *P*-450 enzymes by the Enzyme Commission (June 2018)

[Prepared by Ron Caspi]

Cytochrome *P*-450 enzymes (CYPs) are a large family of heme-containing proteins found in all kingdoms of life. The term "*P*-450" is derived from the spectrophotometric peak at the wavelength of the absorption maximum of the enzyme (450 nm) when it is in the reduced state and complexed with carbon monoxide. More than 50,000 distinct CYP proteins have been described.

The CYPs are classified into several groups, the main ones being eukaryotic microsomal enzymes, eukaryotic mitochondrial enzymes, and bacterial enzymes. While most CYPs require electrons that originate from NADPH, almost no such enzyme can receive the electrons directly from NADPH, and a secondary electron transfer protein is involved. The classification of CYPs by the Enzyme Commission is determined by the type of reaction they catalyse and the type of electron donor with which they interact.

For microsomal enzymes, the usual electron donor is EC 1.6.2.4, NADPH-hemoprotein reductase. When the reaction involves monooxygenation and formation of a single molecule of water, the enzyme should be classified under EC 1.14.14: oxidoreductases acting on paired donors, with incorporation or reduction of molecular oxygen, with reduced flavin or flavoprotein as one donor, and incorporation of one atom of oxygen into the other donor (e.g. EC 1.14.14.16, steroid 21-monooxygenase).

Bacterial CYPs usually utilize ferredoxin. These enzymes are classified under EC 1.14.15: oxidoreductases acting on paired donors, with incorporation or reduction of molecular oxygen, with reduced iron-sulfur protein as one donor, and incorporation of one atom of oxygen into the other donor (e.g. EC 1.14.15.8, steroid 15β-monooxygenase).Mitochondrial CYPs utilize a specialized ferredoxin, known as adrenodoxin, as their electron donor, and are thus also classified under EC 1.14.15. (e.g. EC 1.14.15.15, cholestanetriol 26-monooxygenase).

When the reaction involves the formation of two molecules of water, the enzyme should be classified under EC 1.14.19: oxidoreductases acting on paired donors, with incorporation or reduction of molecular oxygen, with oxidation of a pair of donors resulting in the reduction of O_2 to two molecules of water (e.g. EC 1.14.19.52, camalexin synthase).

Exceptions do occur — for example, CYPs from the CYP74 family catalyse dehydration reactions that do not require oxygen or an electron donor and are classified under EC 4.2.1 (e.g. EC 4.2.1.121, colneleate synthase). A number of CYPs catalyse an isomerization reaction and should be classified under the proper sub-subclass for the particular isomerization reaction (e.g. EC 5.3.99.4, prostaglandin-I synthase).

Unfortunately, in the past many CYPs have been misclassified under EC 1.14.13, which should be used for enzymes that use NADH/NADPH as their direct electron source. In the coming months these entries will be reclassified under the proper sub-subclass.