Enzyme Classification and Nomenclature

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Based in part on the previous versions of this eLS article 'Enzyme Classification and Nomenclature' (2001, 2005).

Introductory article

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The variety of different names that had been used for the same enzyme and the fact that some different enzymes were known by the same name necessitated the development of a rational system for their classification and nomenclature. The International Union of Biochemistry devised a system of classification that allows the unambiguous identification of enzymes in terms of the reactions they catalyse. This relies on a numerical system (the EC number) to class enzymes in groups according to the types of reaction catalysed and systematic naming that describes the chemical reaction involved. This is now in widespread use and the official list of enzymes classified can be found at *ExplorEnz – The Enzyme Database* (http://www.enzyme-database.org).

Introduction

The need for a rational nomenclature for enzymes can be seen from the plethora of unhelpful names for enzymes in the earlier literature. Only those who were directly involved might have known the difference between the old yellow enzyme and the new yellow enzyme and what diaphorase, or for that matter DT-diaphorase, catalysed (try EC 1.6.99.1 and EC 1.8.1.4). Similarly, the reaction catalysed by rhodanese (thiosulfate sulfurtransferase: EC 2.8.1.1) was not apparent from its name. An enzyme could be known by several different names and the same name was sometimes used for different enzymes and it was not uncommon to find that researchers were reporting studies on different enzymes with similar names, or the same enzyme under different names.

In trying to bring some order to the chaotic situation of enzyme nomenclature, Dixon and Webb (1958) took a step that was radically different from that used in other branches of nomenclature by classifying enzymes in terms of the reactions they catalysed, rather than by their structures. This system has been adopted and developed by the International Union of Biochemistry and Molecular Biology (IUBMB), through its Joint Commission on Biochemical Nomenclature in association with the International Union of Pure and Applied Chemistry (IUPAC) into the *Enzyme Nomenclature* list of enzymes classified by the reactions they catalyse (the Enzyme List). This has been through several printed editions, the most recent being published in 1992 (Webb, 1992). The complete and regularly updated material is now available at the IUBMB Nomenclature Committee's Enzyme Nomenclature website ExplorEnz (http://www.enzyme-database.org/). These official data also form the basis of enzyme identification in many other databases, including the BioCyc Pathway/Genome Database Collection (2015); Caspi *et al*. (2014), the BRENDA Enzyme Information System (2015); Schomburg *et al*. (2013), the Kyoto Encyclopedia of Genes and Genomes (KEGG) (2015); Kanehisa *et al*. (2014), the Eawag Biocatalysis/Biodegradation Database (EAWAG-BBD (2015), formerly UM-BBD); Gao *et al*. (2010), the NIST Standard Reference Database on the Thermodynamics of Enzyme-Catalyzed Reactions (2015), the SWISSPROT ENZYME (2015) database; Gasteiger et al (2003) and the Protein Data Bank (PDB) (2015); Berman *et al*. (2014). The Enzyme List is continuously updated to accommodate new discoveries and new material is available online as Enzyme Supplements at the ExplorEnz web site. http://www.enzyme-database.org/updates.php. **See also**: **Enzymes: General Properties**; **Enzymes: The Active Site**; **Enzyme Activity and Assays**; **Enzymology Methods**; **Enzyme Specificity and Selectivity**

Detailed rules for naming and classifying enzymes have been formulated. Each enzyme is given a unique identifier, the EC number, which comprises four components. The first of these represents the type of reaction catalysed, as illustrated in **Table 1**, and it is usually a relatively easy matter to assign an enzyme to an overall class. For example, if it oxidises something by reducing $NAD(P)^+$, it is a dehydrogenase classified as EC 1.x.1.–, where the number x refers to the group oxidised: 1 for –CHOH–, 2 for aldehyde or ketone, and so on; however, if it transfers a phosphate, a diphosphate or another phosphate-containing group through its phosphate to another substrate, it is a phosphotransferase classified as EC 2.7.z.–, where z refers to the nature of the acceptor group, and so on. The fourth component is a number that identifies the specific enzyme within that group. Detailed descriptions of the procedures for assigning enzymes to specific classes and subclasses and the rules for systematic enzyme names that have been approved by the IUBMB Nomenclature Committee have been published in Enzyme Nomenclature (Webb, 1992) and this is available online at the ExplorEnz web site http://www.enzyme-database.org/rules.php. The account here has been adapted from the fuller material in that source, which should be consulted if further detail is required.

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Table 1 Enzyme classes and the types of reaction they catalyse[a]

Class number	Class name	Reaction schema
1	Oxidoreductases	$AH_2 + B^+ = A + BH + H^+$ or $AH_2 + B = A + BH_2$
2	Transferases	$AX + B = A + BX$
3	Hydrolases	$A - B + H_2O = AH + BOH$
4	Lyases	$A = B + X - Y = \begin{matrix} A—B \\ \vert \quad \vert \\ X \quad Y \end{matrix}$
5	Isomerases	$A = B$
6	Ligases	$A + B + NTP = A - B + NDP + P$ or $A + B + NTP = A - B + NMP + PP$

[a]Adapted with permission from McDonald AG & Tipton KF (2014) © John Wiley & Co Ltd.

General Classification Structure

The basic layout of the classification entry for each enzyme is described here with some indication of the guidelines followed. Further details of the principles governing the nomenclature of individual enzyme classes are given in the following sections.

EC number

The classification number, which is made up of four numbers separated by periods, identifies the enzyme by the reaction catalysed. It is intended to provide an unambiguous identifier for that enzyme and is also valuable for relating the information to other databases.

Accepted name

The most commonly used name for the enzyme is usually used, provided that it is neither ambiguous nor misleading. A number of generic words indicating reaction types may be used in Accepted names: for example, *dehydrogenase*, *reductase*, *oxidase*, *peroxidase*, *kinase*, *tautomerase*, *deaminase*, *dehydratase*. Where additional information is needed to make the reaction clear, a word or phrase indicating the reaction or a product may be added in parentheses after the second part of the name, for example, (*ADP-forming*), (*dimerising*), (*CoA-acylating*). In the case of dehydrogenases, for example, (NAD^+) may be used to distinguish an enzyme that is specific for this acceptor from others catalysing a similar transformation but using a different acceptor.

Reaction

The actual reaction catalysed is written, where possible, in the form of a 'biochemical' equation 1:

$$A + B = P + Q \qquad (1)$$

This formulation gives no indication of the equilibrium position of the reaction or the net direction of flux through the enzyme *in vivo*. Indeed, in some cases, an enzymatic reaction can proceed in a thermodynamically unfavoured direction in a metabolic pathway because of the effective removal of one of the reactants in a subsequent reaction. The direction chosen for the reaction is, by convention, the same for all the enzymes in a given class, even if this direction has not been demonstrated for all. Frequently, such biochemical equations are neither fully charge-balanced nor mass-balanced.

Notes on Chemical Nomenclature

Although a detailed description of chemical nomenclature is beyond the scope of this article, some comments are necessary because the fearsome names used are often difficult for a biochemist to understand. The aim of the chemist is to be able to name a compound in such a way that anyone who knows the rules of chemical nomenclature can write down its chemical structure and formula from that name. Therefore, it must be unambiguous in terms of all the chemical groups that make up the compound, how and where they are linked together, and the compound's stereochemistry. This does lead to names that are not much help for general use; for example, the neurotransmitter noradrenaline (norepinephrine) has a systematic name (*R*)-4-(2-amino-1-hydroxyethyl)-1,2-benzenediol; the antibiotic benzylpenicillin is [2*S*-(2α,5α,6β)]-3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid; and aspirin is 2-(acetyloxy)benzoic acid.

The basic rules for writing down the systematic name of a compound are, first, to take a basic (or root) structure or its derivative. For example, benzoic acid is the derivative of the root benzene in the case of aspirin. The substituents are then written before it, with the position of each substituent and any stereochemistry being identified. There are several possible modifications of this procedure and it is possible to write more than one systematic name that is more-or-less unambiguous (see, e.g. the alternative names that have been used for noradrenaline in ChemSpider). Variations arise, for example, from the choice of root compound and the order in which the substituents are written. Where systematic names are used for compounds, the enzyme classification system uses the IUPAC system, which uses rather few root compounds and writes the substituents in alphabetical order (e.g. amino before hydroxy before methyl, and so on). The summary given glosses over many of the complexities of systematic chemical nomenclature, and fuller details of the complexities of systematic chemical nomenclature and fuller details of the rules and their application can be found in Favre and Powell (2013) with an older version available online at *IUPAC Nomenclature of Organic Compounds* (1993). A full list of IUPAC and IUBMB recommendations on chemical and biochemical nomenclature can be found at the IUPAC & IUBMB (2013) Nomenclature recommendations web site.

Chemists use fewer root structures than biochemists. For example, biochemists know the amino acid tryptophan and that it can be decarboxylated to tryptamine. They therefore have no trouble with naming the hormone melatonin as *N*-acetyl-5-methoxytryptamine. However, if a chemist does not accept tryptamine as a root structure, the name becomes *N*-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]acetamide. Because the enzyme classification system is primarily designed for biochemists, the biochemical names are frequently used, where these are widely known. However, collaboration with IUPAC ensures that the systematic names can be readily found from these in their literature and a *Glossary* is provided for each entry, where appropriate, to give the IUPAC or alternative names for the compounds referred to. The Glossary can also be accessed separately, at http://www.enzyme-database.org/glossary.php, where the entries are linked to the ChemSpider database (2015); Williams and Tkachenko (2014), to allow their structures to be viewed. The biochemical literature contains many abbreviated or contracted names, such as AdoMet, ATP and GlcNAc, which are frequently used without definition. In order to help those working in other fields, a list of these and their definitions is provided at http://www.enzyme-database.org/abbrev.php.

It should be noted that the systematic names of noradrenaline and melatonin are single 'words', which can contain lots of hyphens in them, and generally systematic names are written as single 'words'. Among the few exceptions to this general rule are acids, including phosphates, as shown by the examples of penicillin and aspirin, where 'acid' is written as a separate word. This also applies to biochemical names, where, for example, creatine phosphate is written as two words, although it is possible to write the compound as a single word by rearranging the name to phosphocreatine. An example of such rearrangement is the name 6-phosphofructokinase for the enzyme (EC 2.7.1.11) that catalyses reaction 2.

$$\text{ATP} + \text{D-fructose 6-phosphate} = \text{ADP} + \text{D-fructose 1,6-bisphosphate} \quad (2)$$

Note that the term bisphosphate is used here rather than diphosphate. In order to avoid confusion, diphosphate is used only for cases where the two phosphates are linked together (as in adenosine diphosphate; ADP), whereas bisphosphates have the two phosphates attached to separate groups in the molecule.

When a substrate name has two words, there is a potential problem using them in enzyme names. Glucose-6-phosphate 1-dehydrogenase (EC 1.1.1.49) catalyses reaction 3.

$$\text{D-glucose 6-phosphate} + \text{NADP}^+ = \text{6-phospho-D-glucono-1,5-lactone} + \text{NADPH} + \text{H}^+ \quad (3)$$

But in order to indicate that the substrate oxidised is glucose 6-phosphate, not just phosphate, an extra hyphen is added to the substrate name in forming the enzyme name.

In denoting stereochemistry, the IUPAC rules prefer the *R*- and *S*- system and this is generally used in enzyme nomenclature. However, in the case of sugars and amino acids and sugars, the D- and L- designations are so well known that they are followed in the enzyme list. The use of italics in chemical names can at first seem rather odd, but the simplest way of thinking about it is to consider how one would look up the name of a compound in an index, for example, *N*-acetyl-5-methoxytryptamine would be found by searching through A for acetyl not N for *N*-acetyl. Clearly, the same applies to *R*- and *S*-isomers. Therefore, the italic can be taken to mean 'do not bother to look under this letter in any index'. Having adopted this way of doing things, it is logical also to use italics for these when they occur in the middle of a name. The exceptions to this general rule are the D- and L- designations, which are not italicised, but are written, by convention, in a smaller size than normal.

Enzyme Classes and Definitions

In the examples given here, the Glossary entries, links to other databases and references have been omitted to save space.

Class 1. Oxidoreductases

This class contains the enzymes catalysing oxidation reactions. Because the oxidation of one group must be accompanied by the reduction of another, they are grouped together as oxidoreductases. The Systematic enzyme name is in the form *donor:acceptor oxidoreductase*. The substrate that is being oxidised is regarded as being the donor. The Accepted name is frequently of the form *donor dehydrogenase*. Although the term *reductase* is sometimes used as an alternative where the reaction is known to proceed in that direction, it is important to remember that the Accepted name does not necessarily define direction in which the reaction is believed to proceed. The term *donor oxidase* is used only when O_2 is the acceptor.

The second figure in the EC number of the oxidoreductases denotes the type of group in the hydrogen-donor substrate that is oxidised or reduced. The third number denotes the hydrogen acceptor: 1 denotes $NAD(P)^+$, 2 a cytochrome, 3 molecular oxygen, 4 a disulfide, 5 a quinone or similar compound, 6 a nitrogenous group, 7 an iron–sulfur protein, and 8 a flavin. The number 98 is used for other known acceptors and 99 is for cases where the physiological acceptor is, as yet, unknown. This last group contains a number of enzymes that have been shown to work with synthetic acceptors, such as 2,6-dichloroindophenol or phenazine methosulfate, but where the physiological acceptor is unknown. It is intended that these should be transferred to more descriptive sub-subclasses when the natural acceptor has been identified.

For subclasses 1.13 and 1.14, a different classification scheme is used, as these enzymes catalyse the incorporation of oxygen into the substrate. The Accepted names are generally monooxygenase or dioxygenase, depending on whether one or two atoms of oxygen are incorporated into the substance oxidised.

Table 2 summarises the structure of Class 1.

Examples

EC	**1.1.1.14**
Accepted name:	L-iditol 2-dehydrogenase
Reaction:	L-iditol + NAD^+ = L-sorbose + NADH + H^+
Other name(s):	polyol dehydrogenase; sorbitol dehydrogenase
Systematic name:	L-iditol:NAD^+ 2-oxidoreductase
Comments:	Also acts on D-glucitol (giving D-fructose) and other closely related sugar alcohols.
EC	**1.14.13.59**
Accepted name:	L-lysine N^6-monooxygenase (NADPH)
Reaction	L-lysine + NADPH + H^+ + O_2 = N^6-hydroxy-L-lysine + $NADP^+$ + H_2O
Other name(s):	lysine N^6-hydroxylase; L-lysine 6-monooxygenase (NADPH) (*ambiguous*)
Systematic name:	L-lysine, NADPH:oxygen oxidoreductase (6-hydroxylating)
Comments:	A flavoprotein (FAD). The enzyme from strain EN 222 of *Escherichia coli* is highly specific for L-lysine; L-ornithine and L-homolysine are, for example, not substrates

Class 2. Transferases

These enzymes transfer a group from one substrate (the donor) to another (the acceptor) according to the general reaction 4:

$$\text{X–Y} + \text{Z} = \text{X} + \text{Y–Z} \quad (4)$$

The Systematic name is in the form *donor:acceptor grouptransferase*. The Accepted names are normally formed according to *acceptor grouptransferase* or *donor grouptransferase*.

Sometimes transferase reactions can be considered in different ways; for example, the general reaction shown may be regarded as a transfer of the group Y from X to Z, and would therefore be termed a Y-transferase. However, it could also be considered as a breaking of the X–Y bond by the introduction of Z. For example, where Z represents phosphate, the process is often referred to as phosphorolysis and the enzyme catalysing the reaction as a *phosphorylase*. Although that may be used in the Accepted name, these enzymes are classified as *phosphotransferases*, for systematic purposes.

The aminotransferase (transaminase) reactions involve the transfer of an $–NH_2$ group and H to a compound containing a carbonyl group, in exchange for the =O of that group (reaction 5).

$$\text{R}^1\text{–CHNH}_2\text{–R}^2 + \text{R}^3\text{–CO–R}^4 = \text{R}^1\text{–CO–R}^2 + \text{R}^3\text{–CHNH}_2\text{–R}^4 \quad (5)$$

Thus, the reaction could be regarded as being an oxidative deamination of the donor (e.g. an amino acid) linked to the reductive amination of the acceptor (e.g. oxo acid). Therefore, these enzymes might be classified as oxidoreductases. However, because the unique distinctive feature of the reaction is the transfer of the amino group, these enzymes are classified as aminotransferases (sub-subclass 2.6.1).

The second figure in the code number of the transferases denotes the general nature of the group transferred (2.1 for a one-carbon group; 2.2 for an aldehydic or ketonic group; 2.3 for an acyl group, etc.) and the third number further specifies that group (2.1.1 methyltransferase; 2.1.2; formyltransferase, etc.). The exception is the case of the enzymes transferring phosphorus-containing groups (subclass 2.7), where the third number specifies the nature of the acceptor group.

Table 3 summarises the structure of Class 2.

Example

EC	**2.1.1.114**
Accepted name:	polyprenyldihydroxybenzoate methyltransferase
xReaction:	*S*-adenosyl-L-methionine + 3,4-dihydroxy-5-*all-trans*-polyprenylbenzoate = *S*-adenosyl-L-homocysteine + 3-methoxy-4-hydroxy-5-*all-trans*-polyprenylbenzoate
Other name(s):	3,4-dihydroxy-5-hexaprenylbenzoate methyltransferase;dihydroxyhexaprenylbenzoate methyltransferase; COQ3 (*gene name*); Coq3 *O*-methyltransferase; DHHB *O*-methyltransferase
Systematic name:	*S*-adenosyl-L-methionine:3,4-dihydroxy-5-*all-trans*-polyprenylbenzoate 3-*O*-methyltransferase

Comments:	This enzyme is involved in ubiquinone biosynthesis. Ubiquinones from different organisms have a different number of prenyl units (e.g.,ubiquinone-6 in *Saccharomyces*, ubiquinone-9 in rat and ubiquinone-10 in human), and thus the natural substrate for the enzymes from different organisms has a different number of prenyl units. However, the enzyme usually shows a low degree of specificity regarding the number of prenyl units. For example, the human COQ3 enzyme can restore biosynthesis of ubiquinone-6 in coq3 deletion mutants of yeast [3]. The enzymes from yeast and rat also catalyse the methylation of 3-demethylubiquinol-6 and 3-demethylubiquinol-9, respectively [2] (this activity is classified as EC 2.1.1.64, 3-demethylubiquinol 3-*O*-methyltransferase)

Class 3. Hydrolases

These enzymes catalyse the hydrolytic cleavage of bonds such as C–O, C–N, C–C and some other bonds, including phosphoric anhydride bonds. The overlapping specificities of many of these enzymes make it difficult to formulate general rules that are applicable to all members of this class. The Systematic name usually takes the form *substrate X-hydrolase*, where X is the group removed by hydrolysis. The Accepted name is, in many cases, formed by the name of the substrate with the suffix *-ase*. It is understood that the name of the substrate with this suffix indicates a hydrolytic enzyme.

Table 2 Class 1. Oxidoreductases (partial list)

EC 1	Oxidoreductases
EC 1.1	Acting on the CH-OH group of donors
EC 1.1.1	With NAD^+ or $NADP^+$ as acceptor
EC 1.1.2	With a cytochrome as acceptor
EC 1.1.3	With oxygen as acceptor
EC 1.1.4	With a disulfide as acceptor
EC 1.1.5	With a quinone or similar compound as acceptor
EC 1.1.9	With a copper protein as acceptor
EC 1.1.98	With other, known, acceptors
EC 1.1.99	With other, unknown, acceptors
EC 1.2	Acting on the aldehyde or oxo group of donors
EC 1.2.1	With NAD^+ or $NADP^+$ as acceptor
EC 1.2.2	With a cytochrome as acceptor
EC 1.2.3	With oxygen as acceptor
EC 1.2.4	With a disulfide as acceptor
EC 1.2.5	With a quinone or similar compound as acceptor
EC 1.2.7	With an iron-sulfur protein as acceptor
EC 1.2.99	With other, unknown, acceptors
EC 1.3	Acting on the CH-CH group of donors
EC 1.3.1	With NAD^+ or $NADP^+$ as acceptor
EC 1.3.2	With a cytochrome as acceptor
EC 1.3.3	With oxygen as acceptor
EC 1.3.4	With a disulfide as acceptor
EC 1.3.5	With a quinone or related compound as acceptor
EC 1.3.7	With an iron-sulfur protein as acceptor
EC 1.3.8	With a flavin as acceptor
EC 1.3.98	With other, known, acceptors
EC 1.3.99	With other, unknown, acceptors
EC 1.4	Acting on the CH-NH_2 group of donors
EC 1.4.1	With NAD^+ or $NADP^+$ as acceptor
EC 1.4.2	With a cytochrome as acceptor
EC 1.4.3	With oxygen as acceptor
EC 1.4.4	With a disulfide as acceptor
EC 1.4.5	With a quinone or other compound as acceptor
EC 1.4.7	With an iron-sulfur protein as acceptor
EC 1.4.9	With a copper protein as acceptor
EC 1.4.99	With other, unknown, acceptors
EC 1.5	Acting on the CH-NH group of donors
EC 1.5.1	With NAD^+ or $NADP^+$ as acceptor
EC 1.5.3	With oxygen as acceptor
EC 1.5.4	With a disulfide as acceptor
EC 1.5.5	With a quinone or similar compound as acceptor
EC 1.5.7	With an iron-sulfur protein as acceptor
EC 1.5.8	With a flavin or flavoprotein as acceptor
EC 1.5.99	With other, unknown, acceptors
EC 1.6	Acting on NADH or NADPH
EC 1.6.1	With NAD^+ or $NADP^+$ as acceptor
EC 1.6.2	With a heme protein as acceptor
EC 1.6.3	With oxygen as acceptor
EC 1.6.4	With a disulfide as acceptor (deleted sub-subclass)
EC 1.6.5	With a quinone or similar compound as acceptor
EC 1.6.6	With a nitrogenous group as acceptor
EC 1.6.7	With an iron-sulfur protein as acceptor (deleted sub-subclass)
EC 1.6.8	With a flavin as acceptor (deleted sub-subclass)
EC 1.6.99	With other, unknown, acceptors
EC 1.7	Acting on other nitrogenous compounds as donors
EC 1.7.1	With NAD^+ or $NADP^+$ as acceptor
EC 1.7.2	With a cytochrome as acceptor
EC 1.7.3	With oxygen as acceptor
EC 1.7.5	With a quinone or similar compound as acceptor
EC 1.7.6	With a nitrogenous group as acceptor
EC 1.7.7	With an iron-sulfur protein as acceptor
EC 1.7.9	With a copper protein as acceptor
EC 1.7.99	With other, unkown, acceptors
EC 1.8	Acting on a sulfur group of donors
EC 1.8.1	With NAD^+ or $NADP^+$ as acceptor
EC 1.8.2	With a cytochrome as acceptor
EC 1.8.3	With oxygen as acceptor
EC 1.8.4	With a disulfide as acceptor
EC 1.8.5	With a quinone or similar compound as acceptor
EC 1.8.6	With a nitrogenous group as acceptor (deleted sub-subclass)
EC 1.8.7	With an iron-sulfur protein as acceptor
EC 1.8.98	With other, known, acceptors

Table 3 Class 2. Transferases

EC 2	Transferases
EC 2.1	Transferring one-carbon groups
EC 2.1.1	Methyltransferases
EC 2.1.2	Hydroxymethyl-, formyl- and related transferases
EC 2.1.3	Carboxy- and carbamoyltransferases
EC 2.1.4	Amidinotransferases
EC 2.2	Transferring aldehyde or ketonic groups
EC 2.2.1	Transketolases and transaldolases
EC 2.3	Acyltransferases
EC 2.3.1	Transferring groups other than aminoacyl groups
EC 2.3.2	Aminoacyltransferases
EC 2.3.3	Acyl groups converted into alkyl groups on transfer
EC 2.4	Glycosyltransferases
EC 2.4.1	Hexosyltransferases
EC 2.4.2	Pentosyltransferases
EC 2.4.99	Transferring other glycosyl groups
EC 2.5	Transferring alkyl or aryl groups, other than methyl groups
EC 2.5.1	Transferring alkyl or aryl groups, other than methyl groups (only sub-subclass identified to date)
EC 2.6	Transferring nitrogenous groups
EC 2.6.1	Transaminases
EC 2.6.2	Amidinotransferases (deleted sub-subclass)
EC 2.6.3	Oximinotransferases
EC 2.6.99	Transferring other nitrogenous groups
EC 2.7	Transferring phosphorus-containing groups
EC 2.7.1	Phosphotransferases with an alcohol group as acceptor
EC 2.7.2	Phosphotransferases with a carboxy group as acceptor
EC 2.7.3	Phosphotransferases with a nitrogenous group as acceptor
EC 2.7.4	Phosphotransferases with a phosphate group as acceptor
EC 2.7.5	Phosphotransferases with regeneration of donors, apparently catalysing intramolecular transfers (deleted sub-subclass)
EC 2.7.6	Diphosphotransferases
EC 2.7.7	Nucleotidyltransferases
EC 2.7.8	Transferases for other substituted phosphate groups
EC 2.7.9	Phosphotransferases with paired acceptors
EC 2.7.10	Protein-tyrosine kinases
EC 2.7.11	Protein-serine/threonine kinases
EC 2.7.12	Dual-specificity kinases (those acting on Ser/Thr and Tyr residues)
EC 2.7.13	Protein-histidine kinases
EC 2.7.14	Protein-arginine kinases
EC 2.7.99	Other protein kinases
EC 2.8	Transferring sulfur-containing groups
EC 2.8.1	Sulfurtransferases
EC 2.8.2	Sulfotransferases
EC 2.8.3	CoA-transferases
EC 2.8.4	Transferring alkylthio groups
EC 2.9	Transferring selenium-containing groups
EC 2.9.1	Selenotransferases
EC 2.10	Transferring molybdenum- or tungsten-containing groups
EC 2.10.1	Molybdenumtransferases or tungstentransferases with sulfide groups as acceptors

Hydrolytic enzymes might be classified as transferases, because hydrolysis itself can be regarded as transfer of a specific group to water as the acceptor. Yet, in most cases, the reaction with water as the acceptor was discovered earlier and is considered as the main physiological function of the enzyme. This is why such enzymes are classified as hydrolases rather than as transferases.

The second number indicates the nature of the bond hydrolysed, and the third normally specifies the nature of the substrate, for example, in the esterases the *carboxylic ester hydrolases* (3.1.1), *thiolester hydrolases* (3.1.2), *phosphoric monoester hydrolases* (3.1.3); in the glycosidases, the *glycosidases hydrolysing* O- *and* S-*glycosyl compounds* (3.2.1) and N-*glycosidases* (3.2.2).

The peptidases (also termed proteases, proteinases , proteolytic enzymes or peptide hydrolases) in subclass 3.4. cannot be accommodated within the general scheme used for other enzymes. It is not even possible to give them meaningful EC numbers or unambiguous Systematic names because of variable specificities and great similarities between the actions of different peptidases. These enzymes were grouped into two sets of sub-subclasses, the endopeptidases (3.4.21 to 3.4.25 and 3.4.99) and exopeptidases (3.4.11 to 3.4.19), with the third number also depending on the catalytic mechanism. However, this proved inadequate because of the large number of peptidases catalysing similar reactions and it was decided to cease adding new peptidases to the list but to rely on the specific MEROPS (2014) database which uses an entirely different classification system for these enzymes (Rawlings et al., 2014). Entries for peptidases that were already in the Enzyme List have been retained, with links to MEROPS. **See also**: **Proteases**

Table 4 summarises the structure of Class 3.

Examples

EC	**3.1.1.3**
Accepted name:	triacylglycerol lipase
Reaction:	triacylglycerol + H_2O = diacylglycerol + a carboxylate

Other name(s):	lipase (*ambiguous*); butyrinase; tributyrinase; Tween hydrolase; steapsin; triacetinase; tributyrin esterase; Tweenase; amno N-AP; Takedo 1969-4-9; Meito MY 30; Tweenesterase; GA 56; capalase L; triglyceride hydrolase; triolein hydrolase; tween-hydrolyzing esterase; amano CE; cacordase; triglyceridase; triacylglycerol ester hydrolase; amano P; amano AP; PPL; glycerol-ester hydrolase; GEH; meito Sangyo OF lipase; hepatic lipase; lipazin; post-heparin plasma protamine-resistant lipase; salt-resistant post-heparin lipase; heparin releasable hepatic lipase; amano CES; amano B; tributyrase; triglyceride lipase; liver lipase; hepatic monoacylglycerol acyltransferase
Systematic name:	triacylglycerol acylhydrolase
Comments:	The pancreatic enzyme acts only on an ester–water interface; the outer ester links are preferentially hydrolysed
EC	**3.1.2.23**
Accepted name:	4-hydroxybenzoyl-CoA thioesterase
Reaction:	4-hydroxybenzoyl-CoA + H_2O = 4-hydroxybenzoate + CoA
Systematic name:	4-hydroxybenzoyl-CoA hydrolase
Comments:	This enzyme is part of the bacterial 2,4-dichlorobenzoate degradation pathway

Class 4. Lyases

These enzymes cleave C–C, C–O, C–N and other bonds by means other than hydrolysis or oxidation. They differ from other enzymes in that two substrates may be involved in one reaction direction but only one in the other. When they act on the single substrate, the reaction can be regarded as an internal transfer in which a molecule is eliminated, leaving double bonds or rings. The Systematic name is formed according to the pattern *substrate group-lyase*. The hyphen is an important part of the name which, to avoid confusion, should not be omitted, for example, *hydro-lyase* not 'hydrolyase'. In the Accepted names, expressions such as *decarboxylase* or *aldolase* (in case of elimination of CO_2 or aldehyde, respectively) are used. *Dehydratase* is used for those enzymes catalysing the elimination of water. In cases where the reverse reaction is much more important, or the only one demonstrated, *synthase* (not synthetase) may be used in the name. Although the term SYNTHETASE has sometimes been used in the names of enzymes from this class, the usage is discouraged in order to prevent confusion with enzymes from Class 6 (see subsequent text).

Various subclasses of the lyases include pyridoxal-phosphate enzymes that catalyse the elimination of a β- or γ-substituent from an α-amino acid, followed by a replacement of this substituent by some other group. In the overall replacement reaction, no unsaturated end product is formed; therefore, these enzymes might formally be classified as *alkyltransferases* (EC 2.5.1.–). However, there is ample evidence that the replacement is a two-step reaction involving the transient formation of enzyme-bound α,β- (or β,γ-)unsaturated amino acids. According to the rule that the first reaction is indicative for classification, these enzymes are correctly classified as *lyases*. Examples are *tryptophan synthase* (EC 4.2.1.20) and *cystathionine* β-*synthase* (EC 4.2.1.22). The second number indicates the bond broken: 4.1 enzymes are carbon–carbon lyases, 4.2 enzymes are carbon–oxygen lyases, and so on. The third number 4 gives further information on the group eliminated (e.g. CO_2 in 4.1.1 and H_2O in 4.2.1).

Table 5 summarises the structure of Class 4.

Example

EC	**4.1.2.46**
Accepted name:	aliphatic (*R*)-hydroxynitrile lyase
Reaction:	(2*R*)-2-hydroxy-2-methylbutanenitrile = cyanide + butan-2-one
Other name(s):	(*R*)-HNL; (*R*)-oxynitrilase; (*R*)-hydroxynitrile lyase; *LuHNL*
Systematic name:	(2*R*)-2-hydroxy-2-methylbutanenitrile butan-2-one-lyase (cyanide forming)
Comments:	The enzyme contains Zn^{2+} [1]. The enzyme catalyses the stereoselective synthesis of aliphatic (*R*)-cyanohydrins [1]. No activity towards mandelonitrile and 4-hydroxymandelonitrile [5]. Natural substrates for the (*R*)-oxynitrilase from *Linum usitatissimum* are acetone and butan-2-one, which are the building blocks of the cyanogen glycosides in Linum, linamarin and lotaustralin, or linustatin and neolinustatin, respectively [4]

Class 5. Isomerases

These enzymes catalyse geometric or structural changes within one molecule. According to the type of isomerism involved, they may be called *racemases*, *epimerases*, cis–trans-*isomerases*, *isomerases*, *tautomerases*, *mutases* or *cycloisomerases*. The second number denotes the type of isomerism involved, and the third number the type of substrate. In some cases, the reaction involves an intermolecular oxidoreduction, but because the donor and acceptor groups are in the same molecule they are classified as isomerases rather than as oxidoreductases, even though they may contain firmly bound NAD^+ or $NADP^+$.

Table 6 summarises the structure of Class 5.

Example

EC	**5.1.99.4**
Accepted name:	α-methylacyl-CoA racemase
Reaction:	(2S)-2-methylacyl-CoA = (2R)-2-methylacyl-CoA
Systematic name:	2-methylacyl-CoA 2-epimerase

Table 4 EC 3. Hydrolases (partial list)

EC 3	Hydrolases
EC 3.1	Acting on ester bonds
EC 3.1.1	Carboxylic-ester hydrolases
EC 3.1.2	Thioester hydrolases
EC 3.1.3	Phosphoric-monoester hydrolases
EC 3.1.4	Phosphoric-diester hydrolases
EC 3.1.5	Triphosphoric-monoester hydrolases
EC 3.1.6	Sulfuric-ester hydrolases
EC 3.1.7	Diphosphoric-monoester hydrolases
EC 3.1.8	Phosphoric-triester hydrolases
EC 3.1.11	Exodeoxyribonucleases producing 5′-phosphomonoesters
EC 3.1.12	Exodeoxyribonucleases producing 3′-phosphomonoesters
EC 3.1.13	Exoribonucleases producing 5′-phosphomonoesters
EC 3.1.14	Exoribonucleases producing 3'-phosphomonoesters
EC 3.1.15	Exonucleases that are active with either ribo- or deoxyribonucleic acids and produce 5′-phosphomonoesters
EC 3.1.16	Exonucleases that are active with either ribo- or deoxyribonucleic acids and produce 3′-phosphomonoesters
EC 3.1.21	Endodeoxyribonucleases producing 5′-phosphomonoesters
EC 3.1.22	Endodeoxyribonucleases producing 3′-phosphomonoesters
EC 3.1.23	Site-specific endodeoxyribonucleases: cleavage is sequence specific (deleted sub-subclass)
EC 3.1.24	Site specific endodeoxyribonucleases: cleavage is not sequence specific (deleted sub-subclass)
EC 3.1.25	Site-specific endodeoxyribonucleases that are specific for altered bases
EC 3.1.26	Endoribonucleases producing 5′-phosphomonoesters
EC 3.1.27	Endoribonucleases producing 3′-phosphomonoesters
EC 3.1.30	Endoribonucleases that are active with either ribo- or deoxyribonucleic acids and produce 5′-phosphomonoesters
EC 3.1.31	Endoribonucleases that are active with either ribo- or deoxyribonucleic acids and produce 3′-phosphomonoesters
EC 3.2	Glycosylases
EC 3.2.1	Glycosidases, i.e. enzymes that hydrolyse *O*- and *S*-glycosyl compounds
EC 3.2.2	Hydrolysing *N*-glycosyl compounds
EC 3.2.3	Hydrolysing *S*-glycosyl compounds (deleted sub-subclass)
EC 3.3	Acting on ether bonds
EC 3.3.1	Thioether and trialkylsulfonium hydrolases
EC 3.3.2	Ether hydrolases
EC 3.4	Acting on peptide bonds (peptidases)
EC 3.4.1	α-Amino-acyl-peptide hydrolases (deleted sub-subclass)
EC 3.4.2	Peptidyl-amino-acid hydrolases (deleted sub-subclass)
EC 3.4.3	Dipeptide hydrolases (deleted sub-subclass)
EC 3.4.4	Peptidyl peptide hydrolases (deleted sub-subclass)
EC 3.4.11	Aminopeptidases
EC 3.4.12	Peptidylamino-acid hydrolases or acylamino-acid hydrolases (deleted sub-subclass)
EC 3.4.13	Dipeptidases
EC 3.4.14	Dipeptidyl-peptidases and tripeptidyl-peptidases

(*continued overleaf*)

Table 4 *(Continued)*

EC 3.4.15	Peptidyl-dipeptidases
EC 3.4.16	Serine-type carboxypeptidases
EC 3.4.17	Metallocarboxypeptidases
EC 3.4.18	Cysteine-type carboxypeptidases
EC 3.4.19	Omega peptidases
EC 3.4.21	Serine endopeptidases
EC 3.4.22	Cysteine endopeptidases
EC 3.4.23	Aspartic endopeptidases
EC 3.4.24	Metalloendopeptidases
EC 3.4.25	Threonine endopeptidases
EC 3.4.99	Endopeptidases of unknown catalytic mechanism (sub-subclass is currently empty)
EC 3.5	Acting on carbon–nitrogen bonds, other than peptide bonds
EC 3.5.1	In linear amides
EC 3.5.2	In cyclic amides
EC 3.5.3	In linear amidines
EC 3.5.4	In cyclic amidines
EC 3.5.5	In nitriles
EC 3.5.99	In other compounds
EC 3.6	Acting on acid anhydrides
EC 3.6.1	In phosphorus-containing anhydrides
EC 3.6.2	In sulfonyl-containing anhydrides
EC 3.6.3	Acting on acid anhydrides to catalyse transmembrane movement of substances
EC 3.6.4	Acting on acid anhydrides to facilitate cellular and subcellular movement
EC 3.6.5	Acting on GTP to facilitate cellular and subcellular movement
EC 3.7	Acting on carbon–carbon bonds
EC 3.7.1	In ketonic substances

Comments:	α-methyl-branched acyl-CoA derivatives with chain lengths of more than C_{10} are substrates. Also active towards some aromatic compounds (e.g. ibuprofen) and bile acid intermediates, such as trihydroxycoprostanoyl-CoA. Not active towards free acids

Table 5 Class 4. Lyases

EC 4	Lyases
EC 4.1	Carbon–carbon lyases
EC 4.1.1	Carboxy-lyases
EC 4.1.2	Aldehyde-lyases
EC 4.1.3	Oxo-acid-lyases
EC 4.1.99	Other carbon–carbon lyases
EC 4.2	Carbon–oxygen lyases
EC 4.2.1	Hydro-lyases
EC 4.2.2	Acting on polysaccharides
EC 4.2.3	Acting on phosphates
EC 4.2.99	Other carbon–oxygen lyases
EC 4.3	Carbon–nitrogen lyases
EC 4.3.1	Ammonia-lyases
EC 4.3.2	Amidine-lyases
EC 4.3.3	Amine-lyases
EC 4.3.99	Other carbon–nitrogen lyases
EC 4.4	Carbon–sulfur lyases
EC 4.4.1	Carbon–sulfur lyases (only sub-subclass identified to date)
EC 4.5	Carbon–halide lyases
EC 4.5.1	Carbon–halide lyases (only sub-subclass identified to date)
EC 4.6	Phosphorus–oxygen lyases
EC 4.6.1	Phosphorus–oxygen lyases (only sub-subclass identified to date)
EC 4.7	carbon–phosphorus lyases
EC 4.7.1	carbon–phosphorus lyases (only sub-subclass identified to date)
EC 4.99	Other lyases
EC 4.99.1	Sole sub-subclass for lyases that do not belong in the other subclasses

Class 6. Ligases

These enzymes catalyse the joining together (ligating) of two molecules with the concomitant hydrolysis of a diphosphate bond in ATP or a similar triphosphate. The Systematic enzyme name takes the form *A:B ligase*, *with* a qualifier, if necessary in parentheses to indicate the nucleoside triphosphate involved. Because ATP, for example, may be converted to ADP or AMP in the reaction, it is the product that is specified, for example, (*ADP-forming*) or (*AMP-forming*). The Accepted name often takes the form A–B ligase or A–B synthase, which emphasises the synthetic nature of the reaction. The name synthetase is no longer used, but may be found under other names.

The second number indicates the bond formed: 6.1 for C–O bonds (e.g., enzymes acylating tRNA), 6.2 for C–S bonds (acyl-CoA derivatives), etc. Sub-subclasses are only in use in the C–N ligases (6.3), which include the amide synthases (6.3.1), the peptide synthases (6.3.2), enzymes forming heterocyclic rings (6.3.3), and so on.

Table 7 summarises the structure of Class 6.

Example

EC	**6.2.1.1**
Accepted name:	acetate-CoA ligase
Reaction:	ATP + acetate + CoA = AMP + diphosphate + acetyl-CoA
Other name(s):	acetyl-CoA synthetase; acetyl activating enzyme; acetate thiokinase; acyl-activating enzyme; acetyl coenzyme A synthetase; acetic thiokinase; acetyl CoA ligase; acetyl CoA synthase; acetyl-coenzyme A synthase; short chain fatty acyl-CoA synthetase; short-chain acyl-coenzyme A synthetase; ACS
Systematic name:	acetate:CoA ligase (AMP-forming)
Comments:	Also acts on propanoate and propenoate

Finding Information in ExplorEnz

ExplorEnz is a relational database of the IUBMB Enzyme List. One can search by EC number, name substrate or any other selected word in each or all of the entry fields. Substring searching of each of its fields, along with full-text searching and Boolean (AND, OR, NOT) filtering is also facilitated. Search results can be tailored to display only fields selected by the user, in formats suitable for screen or printing. Downloads of the database are provided as SQL or XML. The *Quick-Start Guide*, found under the information tab on the ExplorEnz home page contains a description of the searching and download options. The complete *Abbreviations* list and *Glossary* can also be found under this tab, along with the classification rules and an FAQ (frequently asked questions) list on enzyme classification and how to use the database.

Limitations and Problems

Isoenzymes may not be easily accommodated in any system of classification simply in terms of reaction catalysed. For example, there are about 20 different isoenzymes of alcohol dehydrogenase in human liver. These have been organised into broad groups in terms of their electrophoretic mobilities and, more precisely, in terms of their sequences and genetic origin. Members of these

Table 6 Class 5. Isomerases

EC 5	Isomerases
EC 5.1	Racemases and epimerases
EC 5.1.1	Acting on amino acids and derivatives
EC 5.1.2	Acting on hydroxy acids and derivatives
EC 5.1.3	Acting on carbohydrates and derivatives
EC 5.1.99	Acting on other compounds
EC 5.2	*cis–trans*-Isomerases
EC 5.2.1	*cis–trans*-Isomerases (only sub-subclass identified to date)
EC 5.3	Intramolecular oxidoreductases
EC 5.3.1	Interconverting aldoses and ketoses, and related compounds
EC 5.3.2	Interconverting keto- and enol-groups
EC 5.3.3	Transposing C=C bonds
EC 5.3.4	Transposing S–S bonds
EC 5.3.99	Other intramolecular oxidoreductases
EC 5.4	Intramolecular transferases
EC 5.4.1	Transferring acyl groups
EC 5.4.2	Phosphotransferases (phosphomutases)
EC 5.4.3	Transferring amino groups
EC 5.4.4	Transferring hydroxy groups
EC 5.4.99	Transferring other groups
EC 5.5	Intramolecular lyases
EC 5.5.1	Intramolecular lyases (only sub-subclass identified to date)
EC 5.99	Other isomerases
EC 5.99.1	Sole sub-subclass for isomerases that do not belong in the other subclasses

Table 7 Class 6. Lyases

EC 6	Ligases
EC 6.1	Forming carbon–oxygen bonds
EC 6.1.1	Ligases forming aminoacyl-tRNA and related compounds
EC 6.1.2	Acid–alcohol ligases (ester synthases)
EC 6.2	Forming carbon–sulfur bonds
EC 6.2.1	Acid–thiol ligases
EC 6.3	Forming carbon–nitrogen bonds
EC 6.3.1	Acid–ammonia (or amine) ligases (amide synthases)
EC 6.3.2	Acid–amino-acid ligases (peptide synthases)
EC 6.3.3	Cyclo-ligases
EC 6.3.4	Other carbon–nitrogen ligases
EC 6.3.5	Carbon–nitrogen ligases with glutamine as amido-N-donor
EC 6.4	Forming carbon–carbon bonds
EC 6.4.1	Ligases that form carbon–carbon bonds (only sub-subclass identified to date)
EC 6.5	Forming phosphoric-ester bonds
EC 6.5.1	Ligases that form phosphoric-ester bonds (only sub-subclass identified to date)
EC 6.6	Forming nitrogen–metal bonds
EC 6.6.1	Forming coordination complexes

groups may show different chain-length specificities for primary aliphatic alcohols and also different inhibitor specificities. However, because they all oxidise primary alcohols and have a strong preference towards NAD^+ as the coenzyme, they are all grouped together under the general heading of EC 1.1.1.1. Furthermore, problems also arise from species differences; for example, EC 1.1.1.1 includes NAD^+-dependent alcohol dehydrogenases from all species, although the mammalian liver and yeast enzymes, for example, are profoundly different in structure and behaviour. Only when isoenzymes have very different substrate specificities might classification by function provide the whole solution. For example, liver glucokinase is now recognised to be a member of the hexokinase family of isoenzymes (hexokinase type IV) and is classified as a hexokinase (EC 2.7.1.1), whereas the name glucokinase (EC 2.7.1.2) is specifically recommended for the enzyme from invertebrates and microorganisms that has a high specificity for glucose. In other cases, this problem is addressed by linking the electronic form of the enzyme list to other appropriate databases, based on structural considerations.

Information and Updates

New enzymes and new functions of existing enzymes are being discovered at a rapid pace and work on revising and expanding the list of enzymes is a continuing operation. The current database contains over 5500 enzymes, whereas in 1961 only 712 were recognised. Suggestions for enzymes that should be included, or for revisions and corrections to existing entries, can be submitted electronically using forms available through ExplorEnz, http://www.enzyme-database.org/forms.php. Alternatively, material for all enzyme classes can be sent by e-mail or regular mail to Dr Andrew McDonald (Department of Biochemistry, Trinity College, Dublin 2, Ireland; E-mail: amcdonld@tcd.ie). After these have been checked and considered by the Nomenclature Committee as a whole, they are made available for a one-month period of public review at http://www.enzyme-database.org/newenz.php before being incorporated into the *Enzyme Nomenclature* database.

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