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REVIEW ARTICLE

Update of the WHO/IUIS Allergen Nomenclature Database based on analysis of allergen sequences

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Abstract

The IUIS Allergen Nomenclature Sub-Committee, under the auspices of the World Health Organization and the International Union of Immunological Societies, maintains the systematic nomenclature of allergenic proteins and publishes a database of approved allergen names on its Web site, www.allergen.org. In this paper, we summarize updates of allergen names approved at the meetings of the committee in 2011 through 2013. These changes reflect recent progress in identification, cloning, and sequencing of allergens. The goals of this update were to increase consistency in the classification of allergens, isoallergens, and variants and in the incorporation of the evolutionary classification of proteins into allergen nomenclature, while keeping changes of established names to a minimum in the interest of continuity. Allergens for which names have been updated include respiratory allergens from birch and ragweed pollen, midge larvae, and horse dander; food allergens from peanut, cow's milk, and tomato; and cereal grain allergens. The IUIS Allergen Nomenclature Sub-Committee encourages researchers to use these updated allergen names in future publications.

The official nomenclature of allergenic proteins is based on the Linnaean binominal nomenclature identifying genus and species of all organisms and was first published in 1986 (1) and revised in 1994 (2–6). The allergen nomenclature is maintained by the IUIS Allergen Nomenclature Sub-Committee under the auspices of the World Health Organization (WHO) and the International Union of Immunological Societies (IUIS). The committee maintains the database of approved allergen names (www.allergen.org), which has developed from a plain text list to a fully functional, searchable database. In order to maintain a consistent allergen nomenclature that complies with the guidelines established by the subcommittee, researchers are required to submit newly described allergens to the Allergen Nomenclature Sub-Committee before submitting their manu-

script to a journal for consideration for publication. Submissions are kept confidential by the subcommittee, and no specific information other than the name of the new allergen will be disclosed on the Web site before publication. The submission form is available at www.allergen.org.

Allergen names are composed of an abbreviation of the scientific name of its source (genus: 3–4 letters; species: 1–2 letters) and an Arabic numeral, for example Der p 1 for the first allergen to be described from the house dust mite *Dermatophagoides pteronyssinus*. Originally, new allergens were assigned consecutive numbers. During the past decades, the increase in sequence data together with advances in bioinformatics made it possible to classify allergens into protein families whose members are evolutionary related, have

similar sequences and structures, and are, in some cases, also cross-reactive (7–9). Hence, homologous allergens within a taxonomic order or family are now assigned corresponding numbers whenever possible, in order to reflect evolutionary relationships between allergens from different sources. For instance, in the rose family (Rosaceae), the numbers 1–5 are assigned to Bet v 1-related proteins (e.g., Mal d 1), thaumatin-like proteins (Mal d 2), nonspecific lipid-transfer proteins (Pru p 3), profilins (Mal d 4), and isoflavone reductases (Pyr c 5), respectively. These families of homologous allergens are frequently referred to as groups, although these designations are not part of the official allergen nomenclature. Examples are the group 1 mite allergens (e.g., Der p 1, Blo t 1, Eur m 1), which are papain-like cysteine proteases, and the group 1 grass pollen allergens (e.g., Phl p 1, Lol p 1, Cyn d 1), which are β -expansins. Nevertheless, established numbers are usually not changed to avoid inconsistencies with allergen names used in previous publications or in

allergen-based products used in clinical practice. Bet v 1-related allergens from legumes, for instance, are named Ara h 8 in peanut, Gly m 4 in soybean, and Vig r 1 in mung bean.

Different closely related molecular species of an allergen are named by four digits following the period after the main allergen number. The first two digits designate isoallergens, which are defined as allergens from a single species with similar molecular masses, similar biochemical functions, and sequence identities >67%. The third and fourth digits distinguish different variants of an isoallergen, which are defined as proteins with more than 90% sequence identity. Variants with different nucleotide sequences encoding identical amino acid sequences do not receive individual designations. Both the 67% and the 90% identity thresholds represent arbitrary limits and serve merely as guidelines. Appropriate allergen designations are assigned on a case-by-case basis.

Table 1 Updated nomenclature of Bet v 1 isoallergens and variants. Boldface: updated allergen designations

Previous name	New name	UniProt	Other names	Comment
Bet v 1.0101	Bet v 1.0101	P15494	Bet v 1a	
Bet v 1.0102	Bet v 1.0101	P15494	Bet v 1 clone 224	Identical to Bet v 1.0101
Bet v 1.0103	Bet v 1.0101	P15494	Bet v 1 clone 2230	Identical to Bet v 1.0101
Bet v 1.0201	Bet v 1.0201	P45431	Bet v 1b	
Bet v 1.0301	Bet v 1.0202	P43176	Bet v 1c	
Bet v 1.0401	Bet v 1.0102	P43177	Bet v 1d	
Bet v 1.0402	Bet v 1.0102	P43177	Bet v 1h	Identical to 'Bet v 1.0401'
Bet v 1.0501	Bet v 1.0103	P43178	Bet v 1e	
Bet v 1.0601	Bet v 1.0104	P43179	Bet v 1f	
Bet v 1.0602	Bet v 1.0104	P43179	Bet v 1i	Identical to 'Bet v 1.0601'
Bet v 1.0701	Bet v 1.0105	P43180	Bet v 1g	
Bet v 1.0801	Bet v 1.0106	P43183	Bet v 1j	
Bet v 1.0901	Bet v 1.0203	P43184	Bet v 1k	
Bet v 1.1001	Bet v 1.0107	P43185	Bet v 1l	
Bet v 1.1101	(Deleted)	Q39417	Bet v 1-Sc1	Pathogen-induced expression
Bet v 1.1201	(Deleted)	Q39420	Bet v 1-Sc2	Pathogen-induced expression
Bet v 1.1301	(Deleted)	Q39415	Bet v 1-Sc3	Pathogen-induced expression
Bet v 1.1401	Bet v 1.0204	P43186	Bet v 1m	
Bet v 1.1402	Bet v 1.0204	P43186	Bet v 1n	Identical to 'Bet v 1.1401'
Bet v 1.1501	(Deleted)	Q42499	BVGC11	Genomic sequence
Bet v 1.1502	(Deleted)	Q42499	BVGC31	Genomic sequence
Bet v 1.1601	(Deleted)	Q39425	BVGC181	Genomic sequence
Bet v 1.1701	(Deleted)	Q39426	BVGC21	Genomic sequence
Bet v 1.1801	(Deleted)	Q39427	BVGC25	Genomic sequence
Bet v 1.1901	(Deleted)	Q39428	BVGC34	Genomic sequence
Bet v 1.2001	(Deleted)	Q39429	BVGC45	Genomic sequence
Bet v 1.2101	(Deleted)	Q39430	BVGC63	Genomic sequence
Bet v 1.2201	(Deleted)	Q39431	BVGC681	Genomic sequence
Bet v 1.2301	(Deleted)	O23754	BVGC70	Genomic sequence
Bet v 1.2401	Bet v 1.0108	Q96365	Bet v 1 clone 167	
Bet v 1.2501	Bet v 1.0109	Q96366	Bet v 1 clone 184	
Bet v 1.2601	Bet v 1.0110	Q96367	Bet v 1 clone 2225	
Bet v 1.2701	Bet v 1.0111	Q96368	Bet v 1 clone 2226	
Bet v 1.2801	Bet v 1.0112	P15494 variant F63L	Bet v 1 clone 2227	
Bet v 1.2901	Bet v 1.0113	Q96370	Bet v 1 clone 2229	
Bet v 1.3001	Bet v 1.0114	Q96371	Bet v 1 clone 2301	

Researchers are encouraged to use full isoallergen and variant designations in order to unambiguously identify the allergens they work with. The importance of correct isoallergen/variant designations is highlighted by examples of highly different IgE-binding and T-cell activating properties of closely related isoallergens of Bet v 1 from birch pollen (10) and Der p 2 from house dust mite (11).

Updates of allergen designations

The 1994 revision of the allergen nomenclature represented the first introduction of bioinformatics into the allergen nomenclature, and sequence information became mandatory for the inclusion of new allergens. During the last three decades, bioinformatics has developed at an ever increasing speed and a very large amount of sequence data related to allergens has been generated. Many allergens recorded in the IUIS allergen database were originally submitted with partial sequences or even without associated sequence data. In most cases, full sequences have later become available, which in some cases has led to inconsistencies concerning the numbers assigned to allergen names. Therefore, the IUIS Allergen Nomenclature Sub-Committee aimed to screen the database for such entries and to correct them based on sequences and data from the literature.

The database was manually searched for entries with conspicuous features such as missing sequence data, biochemical names similar to those of other allergens from the same source, or inconsistent allergen numbers compared with homologous allergens from the same taxonomic family. Allergen sequences were analyzed by pairwise and multiple sequence alignments. We found several types of incorrect allergen designations in the database and changed them according to the guidelines described above. A list of updated allergen designations is shown in Tables 1–4. These changes were approved by the IUIS Allergen Nomenclature Sub-Committee at its meetings in the years 2011–2013.

Table 2 Updated nomenclature of pectate lyase allergens from short ragweed (*Ambrosia artemisiifolia*) pollen. Boldface: updated allergen designations

Previous name	New name	UniProt
Amb a 1.0101	Amb a 1.0101	P27759
Amb a 1.0201	Amb a 1.0201	P27760
Amb a 1.0202	Amb a 1.0202	E1XUL3
Amb a 1.0301	Amb a 1.0301	P27761
Amb a 1.0302	Amb a 1.0302	P27761 (variant L48Y)
Amb a 1.0303	Amb a 1.0303	P27761 (variant H392R)
Amb a 1.0304	Amb a 1.0304	E1XUL4
Amb a 1.0305	Amb a 1.0305	E1XUL5
Amb a 1.0401	Amb a 1.0401	P28744
Amb a 1.0402	Amb a 1.0402	E1XUL9
Amb a 2.0101	Amb a 1.0501	P27762
Amb a 2.0102	Amb a 1.0502	E1XUM1

Updated nomenclature of Bet v 1 isoallergens and variants

The major birch pollen allergen, Bet v 1, comprises a large number of isoallergens and variants, of which 36 were recorded in the IUIS allergen database (Table 1). A review of these entries revealed several problems: First, 13 entries referred to gene or cDNA sequences whose expression in pollen had not been demonstrated (12, 13). The sequences of Bet v 1.15–Bet v 1.23 were obtained from genomic DNA without determining their expression profiles (12). Bet v 1.11–Bet v 1.13 were identified in pathogen-infected cell cultures and leaves, while no expression in pollen was shown (13). Hence, the entries Bet v 1.11–Bet v 1.13 and Bet v 1.15–Bet v 1.23 were deleted from the database.

Within the remaining 23 entries, four sets of isoallergens had identical protein sequences but different nucleotide sequences (Bet v 1.0101/02/03, Bet v 1.0401/02, Bet v 1.0601/02, Bet v 1.1401/02). In these cases, only the first

Table 3 Updated nomenclature of *Chironomus thummi thummi* hemoglobin allergens. Boldface: updated allergen designations

Previous name	New name	UniProt	Other names
Chi t 1.0101	Chi t 1.0101	P02229	Hemoglobin component III
Chi t 1.0201	Chi t 1.0201	P02230	Hemoglobin component IV
Chi t 2.0101	Chi t 2.0101	P02221	Hemoglobin component I
Chi t 2.0102	Chi t 2.0102	P02221 (variant A113T)	Hemoglobin component IA
Chi t 3.0101	Chi t 3.0101	P02222	Hemoglobin component II-beta
Chi t 4.0101	Chi t 4.0101	P02231	Hemoglobin component IIIA
Chi t 5.0101	Chi t 3.0201	P02224	Hemoglobin component VI
Chi t 6.0101	Chi t 3.0301	P02226	Hemoglobin component VIIA
Chi t 6.0201	Chi t 3.0401	P02223	Hemoglobin component IX
Chi t 7*	Chi t 3.0501	P12548	Hemoglobin component VIIB-3
Chi t 7*	Chi t 3.0601	P84296	Hemoglobin component VIIB-4
Chi t 7*	Chi t 3.0701	P84298	Hemoglobin component VIIB-5/9
Chi t 7*	Chi t 3.0702	P12549	Hemoglobin component VIIB-6
Chi t 7*	Chi t 3.0801	P12550	Hemoglobin component VIIB-7
Chi t 8.0101	Chi t 3.0901	P02227	Hemoglobin component VIII
Chi t 9.0101	Chi t 9.0101	P02228	Hemoglobin component X

*The Uniprot entry P02225, previously listed in the IUIS allergen database for Chi t 7, was demerged into 7 entries, 5 from *C. thummi thummi* and 2 from *C. thummi piger*.

Table 4 Other updated allergen designations

Source	Previous name	New name	Uniprot acc. no.	Biochemical name
High sequence identity to another allergen from the same source <i>Arachis hypogaea</i> (peanut)	Ara h 4.0101	Ara h 3.0201	Q9SQH7	11S globulin; legumin; glycinin
High sequence identity to a homologous allergen from another source from the same taxonomic family <i>Secale cereale</i> (rye)	Sec c 1.0101	Sec c 38.0101	Q9S8H2	Dimeric α -amylase/trypsin inhibitor
<i>Hordeum vulgare</i> (rye)	Hor v 21.0101	Hor v 20.0101	P80198	γ -Hordein
Duplicate entries <i>Hordeum vulgare</i> (barley)	Hor v 1.0101	Hor v 15.0101	P16968	Monomeric α -amylase inhibitor BMAI-1
<i>Equus caballus</i>	Equ c 5.0101	Equ c 4.0101	P82615	Latherin
Different proteins merged into a single allergen name <i>Bos domesticus</i> (cattle)	Bos d 8	Bos d 8 Bos d 9.0101 Bos d 10.0101 Bos d 11.0101 Bos d 12.0101	– P02662 P02663 P02666 P02668	Whole casein fraction α S1-Casein α S2-Casein β -Casein κ -Casein
Update of botanical nomenclature <i>Solanum lycopersicum</i> (previously <i>Lycopersicon esculentum</i> ; tomato)	Lyc e 1.0101 Lyc e 2.0101 Lyc e 2.0201 Lyc e 3.0101 Lyc e 4.0101	Sola l 1.0101 Sola l 2.0101 Sola l 2.0201 Sola l 3.0101 Sola l 4.0101	Q93YG7 Q547Q0 Q8RVW4 P93224 O49881	Profilin β -Fructofuranosidase β -Fructofuranosidase Nonspecific lipid-transfer protein Pathogenesis-related protein PR-10

named isoallergen designation was kept in the database and the multiple nucleotide sequence accession numbers coding for identical amino acid sequences were associated with these records. The remaining 18 sequences were grouped into two isoallergens: Bet v 1.01 with 14 variants and Bet v 1.02 with four variants. Different variants of each isoallergen showed 91–99% sequence identity, whereas identity between Bet v 1.01 and Bet v 1.02 sequences was 84–89% (Fig. 1A).

Different allergen numbers assigned to closely related allergens from the same source

The first two identified allergens from short ragweed (*Ambrosia artemisiifolia*) pollen were originally termed antigen E and antigen K (14, 15) and later renamed to Amb a 1 and Amb a 2 with the establishment of the IUIS nomenclature system (1). Both allergens belong to the pectate lyase family and show considerable IgE cross-reactivity (16). A sequence alignment yielded 61–70% sequence identity between the ten Amb a 1 variants (corresponding to four isoallergens) and the two Amb a 2 variants (Fig. 1B). Hence, Amb a 2.0101 and Amb a 2.0102 were renamed to Amb a 1.0501 and Amb a 1.0502, as two variants of a fifth Amb a 1 isoallergen (Table 2).

Freeze-dried larvae of the nonbiting midge *Chironomus thummi thummi* used as fish feed can elicit respiratory allergic

reactions to its hemoglobin, which is composed of several distinct proteins originally named CTT I to CTT IX (17) and later designated *Chi t I* (18), following the original allergen nomenclature guidelines (1). As a consequence of the heterogeneous composition of *C. thummi thummi* hemoglobin, the Allergen Nomenclature Sub-Committee assigned a separate allergen name to each hemoglobin component in 2003, creating the allergen designations *Chi t 1*–*Chi t 9*. A multiple sequence alignment of these allergens showed sequence identities ranging from 28% to 99%. Particularly, isoallergens of *Chi t 5*–*Chi t 8* showed 51–63% identity to *Chi t 3.0101* (Fig. 1C). Despite having sequence identities below the 67% threshold, their identical molecular weights and biochemical functions justified the consolidation of these isoallergens into the single allergen name *Chi t 3* (Table 3). The names of *Chi t 1*, *Chi t 2*, *Chi t 4*, and *Chi t 9* remained unchanged. Hence, the number of *C. thummi thummi* hemoglobin allergens was reduced from 9 to 5.

Ara h 3 and Ara h 4 from peanut (*Arachis hypogaea*) are major allergens belonging to the 11S seed storage globulin family. Both were submitted to the Allergen Nomenclature Sub-Committee almost simultaneously with partial sequences and different molecular masses (19, 20). Subsequent molecular cloning revealed that their full-length sequences shared 91% identity, by far exceeding the 67% identity threshold for naming isoallergens. Consequently, Ara h 4.0101 was renamed to Ara h 3.0201 (Table 4).

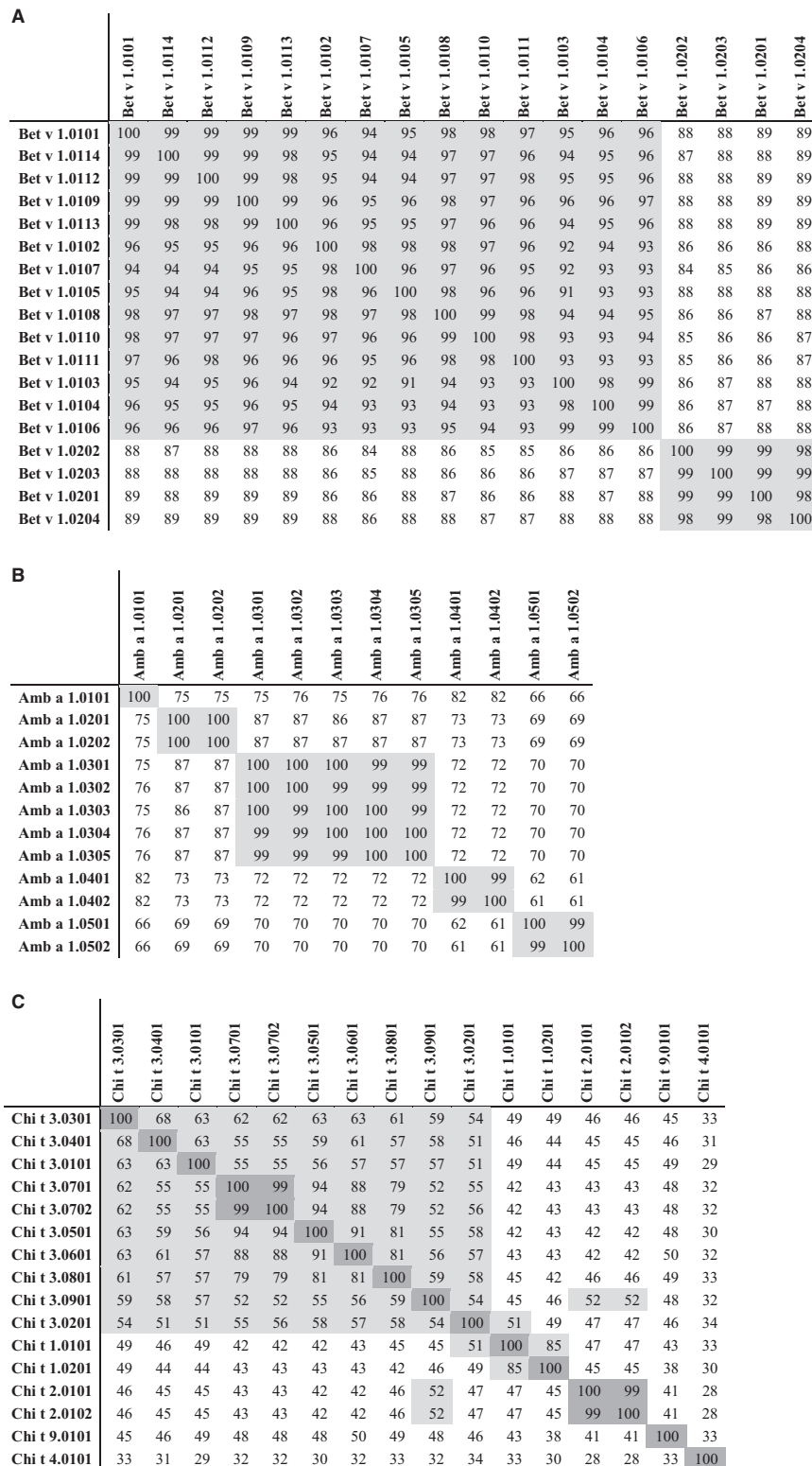


Figure 1 Percentage amino acid sequence identity matrices of Bet v 1 isoallergens and variants (A), Amb a 1 isoallergens and variants (B), and *C. thummi thummi* hemoglobin allergens (C). The values were calculated based on multiple sequence alignments of the amino acid sequences. Updated allergen names according to Tables 1–4 are used. Shadings in A and B indicate >90% identity. Values >50% (light gray) and >95% (dark gray) are shaded in C.

These three examples from ragweed, nonbiting midges, and peanut illustrate that the 67% identity threshold serves only as a reference guideline, whereas the nature of the allergen (biochemical function, molecular structure, molecular weight), in addition to the degree of identity with homologous allergens, takes equal priority for the assignment of allergen names.

Inconsistent allergen numbers regarding protein family memberships

Sec c 1 from rye (*Secale cereale*), a major baker's asthma allergen, is a dimeric bifunctional inhibitor of proteases and α -amylases (21). However, within the grass family (Poaceae), the allergen number 1 is reserved for β -expansin pollen allergens. The only other dimeric α -amylase/protease inhibitor in the IUIS allergen database is Tri a 28 from wheat (*Triticum aestivum*). The sequences of the N-terminal fragment of Sec c 1 and the C-terminal fragment of Tri a 28 overlap by only 16 residues with 38% identity, whereas Tri a 28 is 100% identical to a different dimeric amylase inhibitor from rye (UniProt: C3VWW4). Hence, Sec c 1 showed no close relationship to any other cereal allergens and was renamed to Sec c 38, receiving the next available number within the Poaceae family (Table 4).

Hor v 21 (γ -hordein) from barley (*Hordeum vulgare*) is a member of the γ -prolamin subfamily, which comprises also γ -secalins from rye and γ -gliadins from wheat. The only other γ -prolamin in the allergen database is Sec c 20 with two isoallergens: Sec c 20.0101 (γ -70 secalin) and Sec c 20.0201 (γ -35 secalin). As the allergen number 21 is already reserved for α -/ β -prolamins such as Tri a 21, for the α -/ β -gliadin from wheat, Hor v 21 was renamed to Hor v 20 (Table 4).

Duplicate database entries

Previously, the monomeric α -amylase/protease inhibitor BMAI-1 from barley had been assigned the designations Hor v 1 and Hor v 15. As BMAI-1 is homologous to Tri a 15 from wheat (44% sequence identity), the designation Hor v 15 was maintained and Hor v 1 was deleted (Table 4).

The horse (*Equus caballus*) dander allergens Equ c 4 and Equ c 5 were originally submitted with partial sequence data and molecular masses of 18.7 and 16.7 kDa (22). After the full sequence of horse latherin became available, the partial sequences of both Equ c 4 and Equ c 5 matched this protein. The original description of Equ c 4 and Equ c 5 most likely referred to the glycosylated and nonglycosylated forms of latherin. Thus, the entry Equ c 5 was deleted (Table 4).

Updated nomenclature of casein components

The allergen Bos d 8, casein from cow's (*Bos domesticus*) milk, refers to a mixture of several dissimilar proteins. The casein fraction of milk proteins contains components that belong to two unrelated protein families, one family comprising α S1-, α S2-, and β -caseins, while κ -caseins constitute the

other family (23). Even within the α -/ β -casein family, sequence identities are below 15%. Hence, the entry Bos d 8 was demerged into four separate allergens: Bos d 9.0101 (α S1-casein), Bos d 10.0101 (α S2-casein), Bos d 11.0101 (β -casein), and Bos d 12.0101 (κ -casein; Table 4). The name Bos d 8, which is widely established and has been used in numerous publications and names of commercial diagnostic tests, was kept and designates the whole casein fraction. This example illustrates that the subcommittee takes into consideration not only taxonomic and other scientific aspects but also practical aspects of continuity and public acceptance in its management of the allergen nomenclature.

Adjustment of allergen names to reflect updated taxonomy

In addition to the changes described above, based on sequence similarities and protein family memberships, the IUIS Allergen Nomenclature Sub-Committee changed the designations of tomato allergens from Lyc e 1–Lyc e 4 to Sola l 1–Sola l 4 in order to reflect the establishment of *Solanum lycopersicum* instead of *Lycopersicon esculentum* as the official scientific name of the tomato (24) (Table 4).

Concluding remarks

The WHO/IUIS Allergen Nomenclature Database is continuously updated and supplemented not only with newly submitted allergens, but also with data of already published allergens. The IUIS Allergen Nomenclature Sub-Committee encourages users to notify the committee of missing or inconsistent records in the database and thereby aid in providing a reliable and up-to-date resource of unambiguous allergen names and isoallergen/isoform sequence information for the scientific community. Updates and error reports may be sent to the subcommittee either by using the submission form to be downloaded from www.allergen.org or by directly contacting one of the committee members, whose contact details are published at www.allergen.org.

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Author contributions

C. Radauer drafted the manuscript and performed the greater part of the sequence analyses. A. Nandy contributed to sequence analysis of Bet v 1 and Amb a 1 isoallergens. M. Raulf-Heimsoth and P. Rozynek performed sequence analysis of *Chironomus* allergens. H. Breiteneder, F. Ferreira, R. Goodman, J. N. Larsen, J. Lidholm, A. Pomés, and W. R. Thomas contributed to discussions of several groups of allergens. All authors critically read and approved the manuscript.

Conflicts of interest

All authors have no conflicts of interest to declare.

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