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# Metabolite reporting in large-scale studies within different metabolomics communities:

## DO WE SPEAK THE SAME LANGUAGE?

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### INTRODUCTION

High throughput metabolomic studies are increasing within various scientific communities from analytical chemistry to epidemiology. Therefore, **standardized reporting** is crucial for data sharing. To date, there are no established standards for **metabolite reporting**. Our **objective** was to review the existing practices in terms of metabolite reporting in different scientific communities both in **published results** [1-4] and across **databases** [HMDB V5.0 / PubChem (June 2022) / ChEBI (July 2022) / KNApSAcK (August 2022)].

### MATERIALS & METHODS

We considered **plasma metabolites** reported in **human large-scale** studies from different communities, namely analytical chemistry, medicine and epidemiology [1-4]. We focused only on metabolites reported as **level 1** identification according to the Metabolomics Standard Initiative (MSI) [5].

Published study	Scientific community	Number of metabolites
[1] Gonzalez-Dominguez <i>et al.</i> 2020 <i>Analytical Chemistry</i> , 92: 13767-13775	Analytical chemistry	677
[2] Liu <i>et al.</i> 2020 <i>Analytical Chemistry</i> , 92: 8836-8844	Analytical chemistry	487
[3] Pietzner <i>et al.</i> 2021 <i>Nature Medicine</i> , 27: 471-479	Epidemiology & medicine	585
[4] Yu <i>et al.</i> 2019 <i>American Journal of Epidemiology</i> , 188: 991-1012	Epidemiology & medicine	588

#### Evaluation of metabolite reporting in publications

We applied a data curation workflow on the published lists of annotated metabolites. The workflow consisted of a combination of manual and automatic steps (Figure 1).

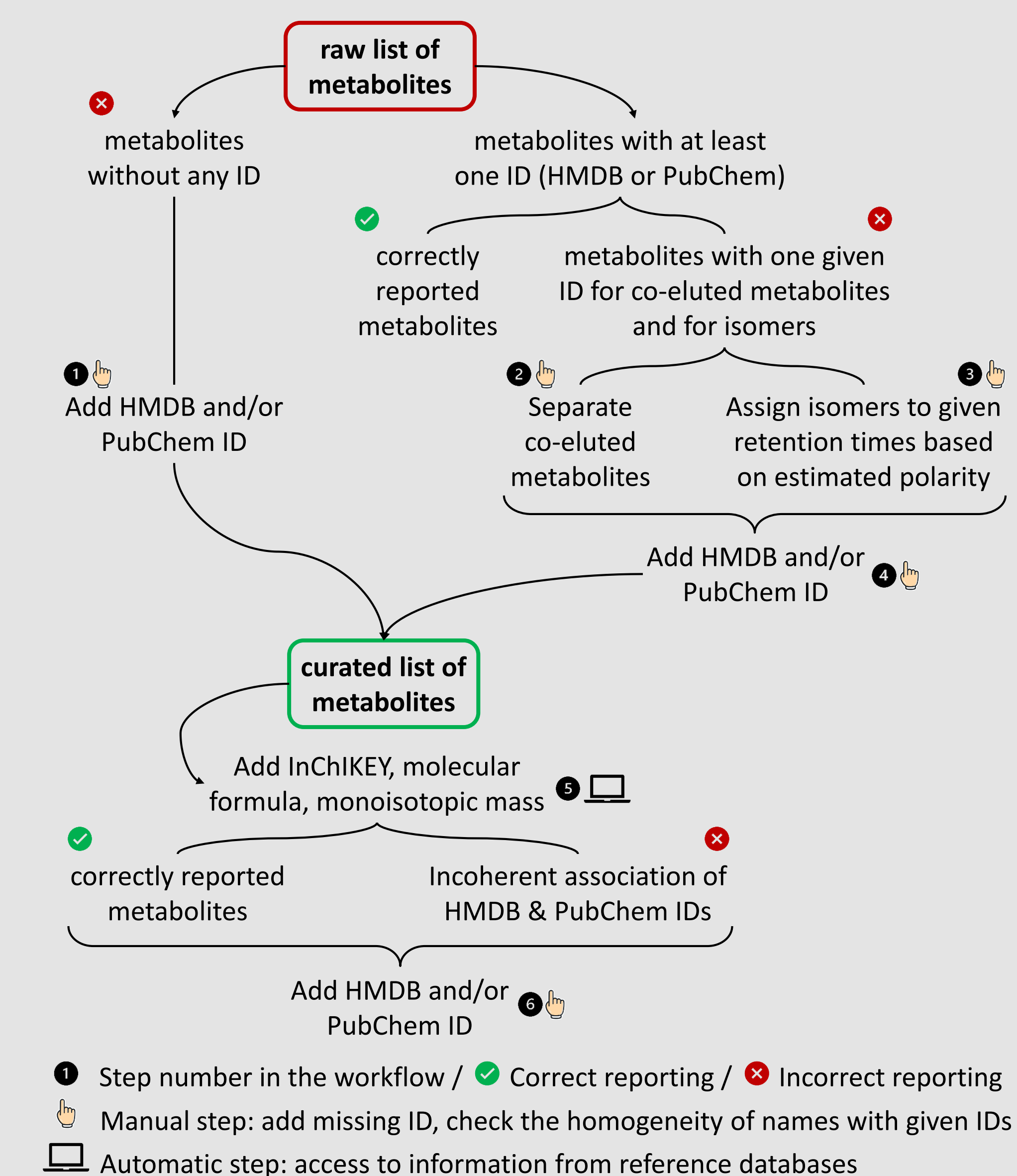


Figure 1. Data curation workflow applied to metabolites reported in published studies [1-4].

#### Evaluation of cross-linking of metabolites across databases

Information was calculated under a Big Data infrastructure (Apache Spark) and Scala programming language with the help of the Metabolomics Semantic DataLake team (Figure 2).

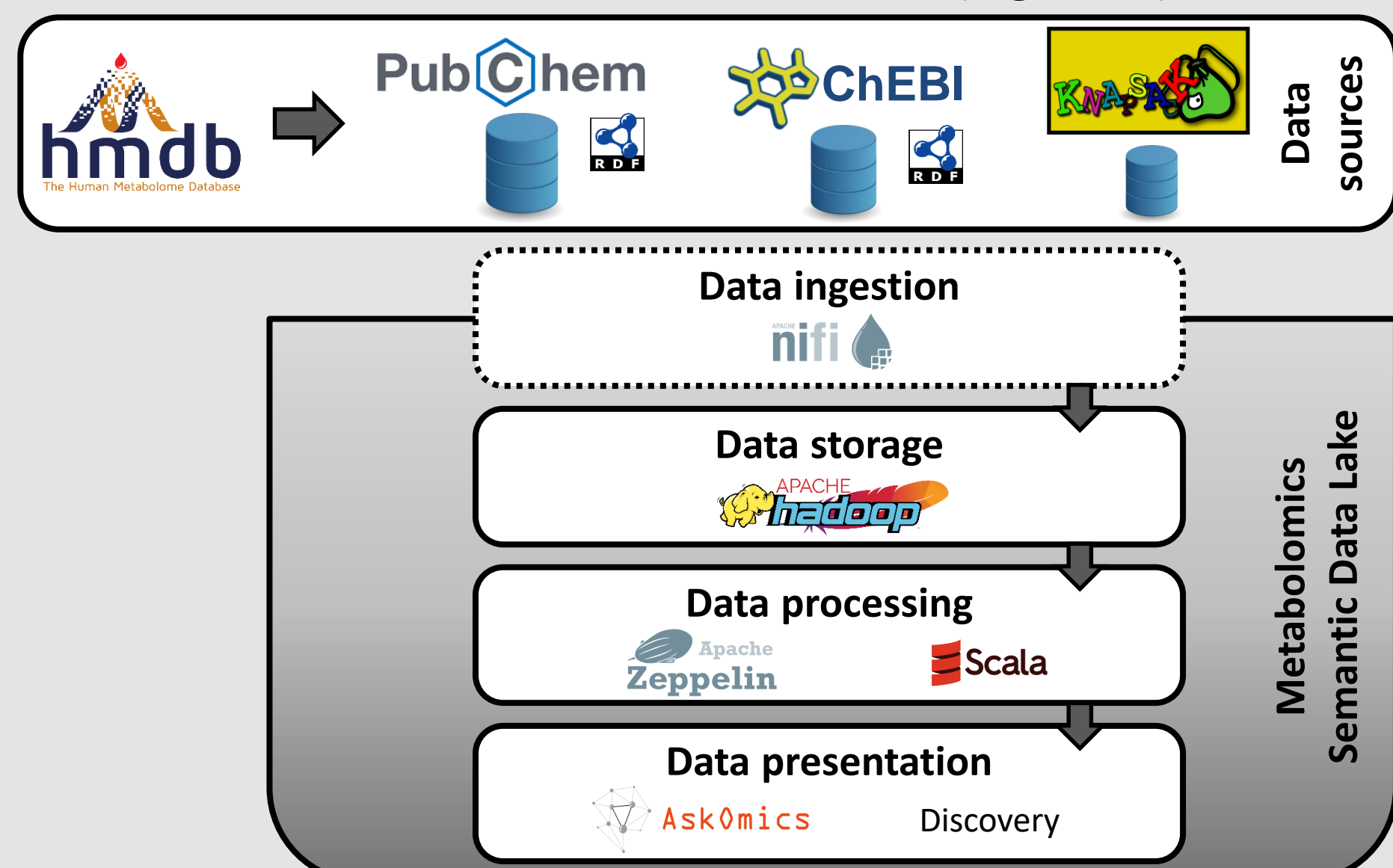


Figure 2. Data flow in a 'Metabolomics Semantic DataLake' infrastructure: Application to assess the cross-linking between metabolites reported in HMDB V5.0 and their reference to PubChem, ChEBI or KNApSAcK.

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### RESULTS

#### Ambiguities observed in published results

Metabolite reporting was not standardized within scientific communities.

- Metabolites were reported using IDs referring to both biological & chemical databases and with identification levels according to the MSI [5]
- Reported common names were different between communities and/or studies
- Available metadata (e.g. MS annotations and other analytical data) were dependent on the scope of the study

Some metabolites were reported with either missing or incoherent information. After data curation (see Figure 1), metabolites were compared between studies using either the names given by the authors or the InChIKeys (Figure 3).

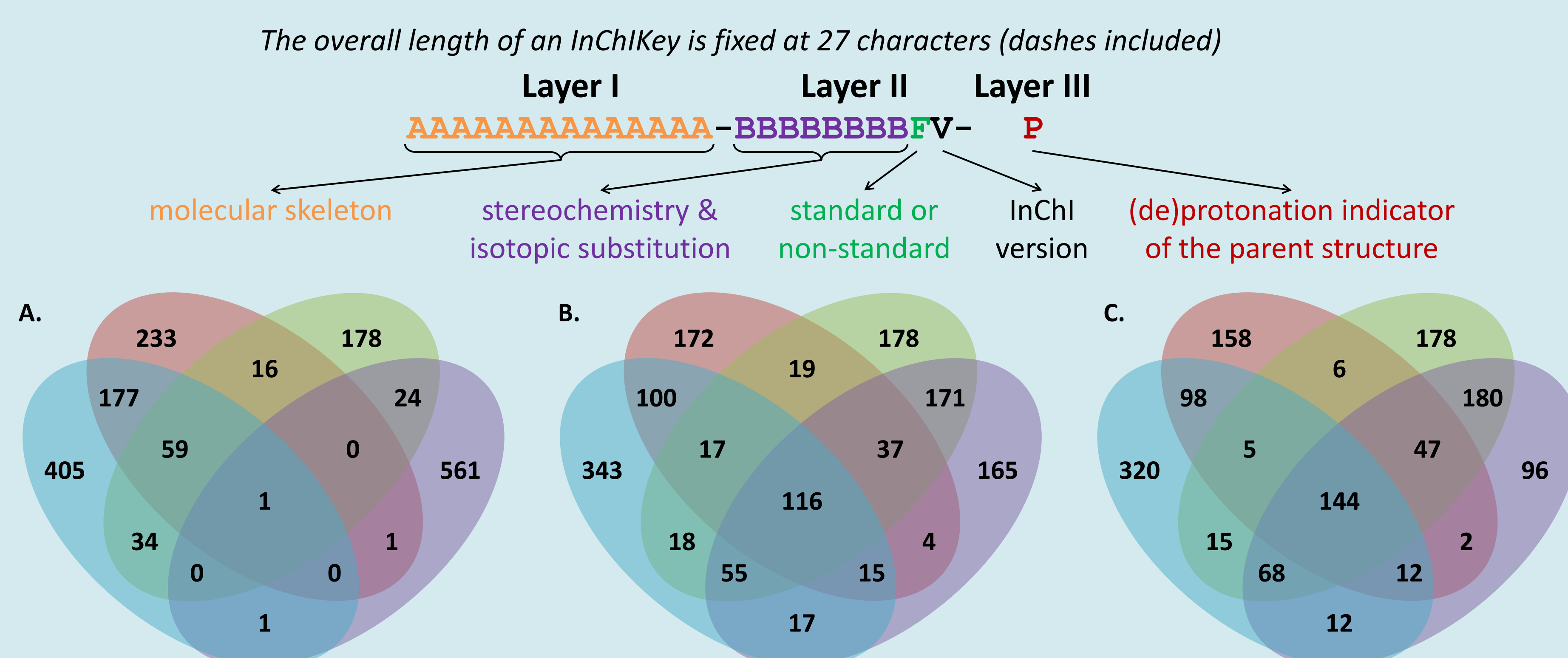


Figure 3. Venn diagrams used to compare metabolites reported in Gonzalez-Dominguez *et al.* 2020 (●), Liu *et al.* 2020 (●), Pietzner *et al.* 2021 (●) & Yu *et al.* 2019 (●) and using A. reported metabolite names, B. metabolite complete InChIKeys, & C. layer I of the InChIKeys.

As shown in Figure 3, using the reported metabolite names, we could spot **only 1** metabolite reported by all 4 studies. However, using the **InChIKey**, the common metabolites were **above 100**. Figures 3B & 3C show the importance of the **isomers'** identification in metabolite reporting. In this case, the InChIKey was the **most suitable identifier** for data inter-comparison.

#### Ambiguities observed across databases

Some metabolites' nomenclatures were incoherent across databases

e.g.  $C_5H_{12}NO_2^+$ : HMDB: **Betaine** (HMDB0000043); PubChem: **Trimethyl glycine** (CID 248); ChEBI: **N,N,N-trimethylglycinium** (CHEBI:41139)

All HMDB entries with ambiguous cross-links to ChEBI, PubChem and KNApSAcK were identified. The percentage of mismatches was independent of the total number of cross-links provided.

- ChEBI: 13 198 HMDB entries with external reference to ChEBI → 4% mismatch (Figure 4A)
- PubChem: 103 593 HMDB entries with external reference to PubChem → 2% mismatch (Figure 4B)
- KNApSAcK: 7 674 HMDB entries with external reference to KNApSAcK → 66% mismatch

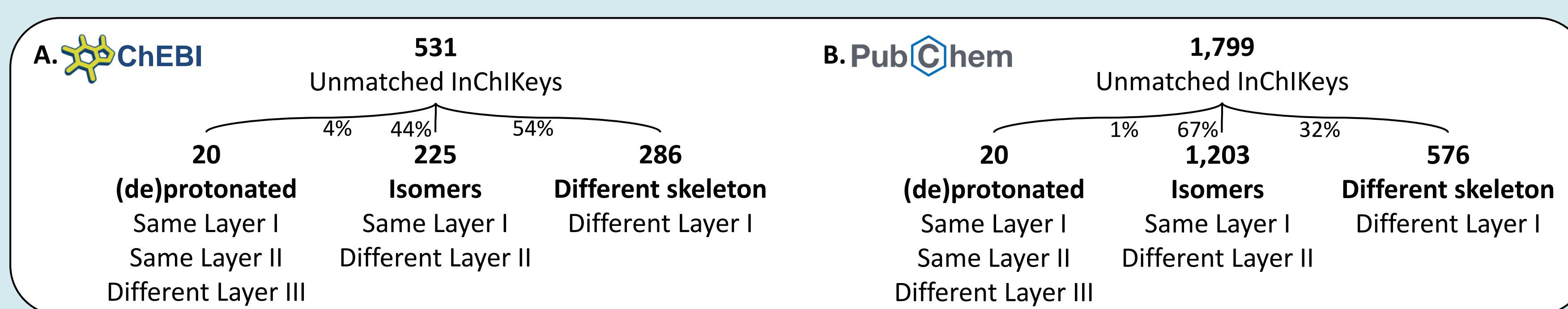


Figure 4. Distribution of HMDB entries with external references to (A) ChEBI and (B) PubChem having unmatched InChIKeys.

Mismatches were classified according to the unmatched InChIKey layer(s)

- (De)Protonation of the core parent structure  
e.g. N6,N6,N6-Trimethyl-L-lysine: HMDB0001325 (a) linked to ChEBI:17311 (b)  
(a) MXNRLFUSFKVQSK-QMMMGPBSA-N (parent structure)  
(b) MXNRLFUSFKVQSK-QMMMGPBSA-O (protonated structure)
- Isomerism, stereochemistry  
e.g.1. D-Xylitol: HMDB0002917 (c) linked to PubChem CID 6912 (d)  
(c) InChI=1S/C5H12O5/c6-1-3(8)5(10)4(9)2-7/h3-10H,1-2H2/t3-,4+,5+ → HEBKCHPVOIAQTA-SCDXWVJYSA-N  
(d) InChI=1S/C5H12O5/c6-1-3(8)5(10)4(9)2-7/h3-10H,1-2H2/t3-,4+,5? → HEBKCHPVOIAQTA-NGQZWQHPSA-N  
e.g.2. Methylcysteine: HMDB0002108 (e) linked to PubChem CID 24417 (f)  
(e) IDIDJDIHTAOVLG-GSVOUGTGSAN → D-isomer  
(f) IDIDJDIHTAOVLG-VKHYHEASAN → L-isomer
- Mismatch between structurally different compounds  
e.g. 4,4-Dimethyl-5a-cholesta-8-en-3b-ol (HMDB0006840) linked to 5,6,7,8-tetrahydrofolylylglutamic acid (CHEBI:27650)

### CONCLUSION

This work will allow providing guidelines for a more effective and reproducible metabolomics data sharing (e.g. use common identifiers such as InChIKey, perform a deep data curation, etc.).

**References:** [1] Gonzalez-Dominguez *et al.* 2020 *Anal. Chem.*, 92: 13767-13775; [2] Liu *et al.* 2020 *Anal. Chem.*, 92: 8836-8844; [3] Pietzner *et al.* 2021 *Nat. Med.*, 27: 471-479; [4] Yu *et al.* 2019 *Am. J. Epidemiol.*, 188: 991-1012; [5] Sumner *et al.* 2007 *Metabolomics*, 3: 211-221.

**Databases:** HMDB V5.0; PubChem (June 2022); ChEBI (July 2022); KNApSAcK (August 2022).