Regulatory Toxicology and Pharmacology 150 (2024) 105641

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Metabolism-based category formation for the prioritisation of genotoxicity hazard assessment for plant protection product residues (Part 4): α-Chloroacetamides

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ARTICLE INFO

Handling Editor: Dr. Martin Van den berg

ABSTRACT

In dietary risk assessment of plant protection products, residues of active ingredients and their metabolites need to be evaluated for their genotoxic potential. The European Food Safety Authority recommend a tiered approach focussing assessment and testing on classes of similar chemicals. To characterise similarity, in terms of metabolism, a metabolic similarity profiling scheme has been developed from an analysis of 69 α-chloroacetamide herbicides for which either Ames, chromosomal aberration or micronucleus test results are publicly available. A set of structural space alerts were defined, each linked to a key metabolic transformation present in the α-chloroacetamide metabolic space. The structural space alerts were combined with covalent chemistry profiling to develop categories suitable for chemical prioritisation via read-across. The method is a robust and reproducible approach to such read-across predictions, with the potential to reduce unnecessary testing. The key challenge in the approach was identified as being the need for metabolism data individual groups of plant protection products as the basis for the development of the structural space alerts.

1. Introduction

The European Food Safety Authority (EFSA) requires an assessment of the genotoxicity potential for active ingredient-associated residues of plant protection products (EFSA Scientific Committee, 2016). The general approach outlined in the available EFSA guidance (EFSA Scientific Committee, 2011) is that such residues should not increase the hazard to humans (and livestock). Thus, within a set of 'similar' residues, a category, a representative number need to have *in vitro* and/or *in vivo* data for gene mutation as well as structural and numerical chromosomal aberration. The availability of such data enables data-gaps within the category to be filled by read-across within this framework, with the minimal data requirements coming from the Ames test (gene mutation) and an *in vitro* micronucleus test (structural and numerical chromosomal aberration). The availability of additional negative *in vivo* data (frequently from the micronucleus test) adds further weight of evidence to the read-across prediction. If a genotoxicity prediction is negative, considering evidence from a quantitative structure-activity model and read-across, then no further experimental testing is required under the EFSA guidance. In contrast, a positive read-across prediction for genotoxicity requires further experimental data to be generated in a tiered approach. For example, if an initial *in vitro* micronucleus test confirms the positive read-across prediction for chromosome damage, an *in vivo* micronucleus test would be triggered.

The key step in the use of the category formation approach is the ability to confidently define 'similarity' between compounds (Enoch et al., 2010; Enoch et al., 2013; OECD, 2007). In terms of the use of category formation in the EFSA genotoxicity workflow noted above, defining similarity is relatively straightforward for potentially genotoxic chemicals. This is due to the key molecular initiating event for DNA-reactive genotoxicity being the formation of a covalent bond between nucleophilic centres in DNA and a compound capable of behaving

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https://doi.org/10.1016/j.yrtph.2024.105641
Received 15 January 2024; Received in revised form 27 March 2024; Accepted 6 May 2024
Available online 7 May 2024

as an electrophile (either directly or after metabolic activation) (Enoch and Cronin, 2010, 2012; Benigni and Bossa, 2008; Benigni et al., 2009; Mekenyan et al., 2004, 2007; Serafimova et al., 2007). The associated chemistry can be encoded easily as structural alert-based *in silico* profilers that enable compounds to be assigned to a category based on the presence of a common alert. In contrast, defining similarity between compounds that lack an alert for DNA reactivity is more challenging due to the lack of such key structural features (Schultz et al., 2018).

Recent research has developed the "structural space alerts" concept to address the similarity between plant protection residues that lack an alert for either covalent protein or DNA reactivity (Enoch et al., 2022a, 2022b, 2023). This concept utilises the metabolism data available in the Draft Assessment Report/Renewal Assessment Report (DAR/RAR) documents of plant protection products (available from the EFSA website) to enable category formation to be based on the presence of a set of common metabolic pathways were present in the analogues within the category. It is important to note that metabolic similarity has been suggested as being a key measure of similarity when making read-across predictions within a regulatory environment (Gadaleta et al., 2020; Yordanova et al., 2021; Boyce et al., 2022). Initial development of the structural space alert concept was based on an analysis of sulphonylurea herbicides and triazole fungicides, with this work defining alerts that defined common scaffolds within the available metabolism data (Enoch et al., 2022a, 2022b). The limitation being that the resulting structural space alerts were not explicitly linked to individual metabolic transformation (as defined from *in vivo* rat metabolism). This led to the resulting categories needing sub-categorisation based on expert judgement to ensure the Target and the analogues all underwent the same set of metabolic transformations. More recent work using the strobilurin fungicides addressed this shortcoming in the structural space alert concept in that each alert was explicitly linked to a metabolic transformation (Enoch et al., 2023). The linkage between structural space alert and metabolic transformation resulted in categories that did not require sub-categorisation via expert judgement, offering a significant improvement in the transparency and repeatability of the approach. Given these advantages, the aim of the current study was to extend the structural space alert concept to the α-chloroacetamide herbicides, using the protocol outlined for the strobilurin fungicides in which each structural space alert was explicitly linked to a metabolic transformation. The concept is exemplified using a case study of how the structural space alerts can be used to fill a data-gap via read-across.

2. Method

2.1. Dataset

The publicly available DAR documents were used to compile six α-chloroacetamide herbicide active ingredients and their metabolites as identified in the rat. In addition, data for a further five active ingredients and their metabolites were compiled from historical data from the industrial co-authors of this study. This led to a dataset of 69 α-chloroacetamide herbicides for which genotoxicity data were extracted for all compounds that had been directly tested in either the Ames test, *in vitro* chromosomal aberration assay or the *in vivo* micronucleus test. All compounds that were identified as being positive in the *in vitro* chromosomal aberration assay had additional data from the *in vivo* micronucleus test showing them to be negative. Importantly, the final dataset expanded the chemical space for the α-chloroacetamide herbicides compared to the available data in the publicly available EFSA genotoxicity dataset (available from zenodo.org/doi/10.5281/zenodo.602287). The dataset, termed the 'α-chloroacetamide genotoxicity dataset' contained the following test results (*in vitro* assays with S9 fraction, Ames tests in the standard battery).

- Ames: 69 compounds (all negative)
- *In vitro* chromosomal aberration: 56 compounds (39 negative, 16 positive, 1 equivocal)
- *In vivo* micronucleus: 39 compounds (all negative)

All chemical structures and associated genotoxicity data are available in the Supplementary Information.

2.2. Metabolic similarity profiling scheme

The development of the metabolic similarity profiling scheme utilised the same protocol as previously published (Enoch et al., 2023) and is summarised in the following three steps.

1. Definition of the metabolic maps for the α-chloroacetamide herbicides: This analysis involved inspection of the available metabolism data in the DAR documents to identify metabolic transformations common to this class of compounds. These metabolic transformations were hydroxylation, dealkylation, glutathione conjugation, hydrolysis/oxidation, and de-halogenation reactions. The most common reactions occurring on the reactive α-chloroacetamide moiety (these being glutathione conjugation, hydrolysis/oxidation, and de-halogenation). These pathways were identified as being major or minor based on the conclusions of the authors of the DAR documents.
2. Scaffold identification: Three key scaffolds were identified for the α-chloroacetamide herbicides. These being based on the difference in metabolism of the aromatic ring system identified in step 1. These scaffolds were termed: benzene, thiophene and styrene. However, they also encompassed attached amide moiety as this was a common structural feature present in all compounds in the dataset (parent and residues).
3. Structural space alert identification: Common sub-structures were then identified for each of the scaffolds identified in step 2 using the metabolic maps developed in step 1. These sub-structures were defined as structural space alerts that defined the atom/atoms on the scaffold upon which the metabolic transformation identified in the metabolic map occurred.

2.3. Chemical profiling

Chemicals were profiled using the profiling schemes within the OECD QSAR Toolbox (V4.1.1). A subset of the available profilers was utilised based on the results of a previous study into their suitability for read-across predictions within the plant protection chemical space (Enoch et al., 2022a, 2022b, 2023). These profilers were (CA is chromosomal aberration and MNT is the micronucleus test).

- DNA alerts for AMES, CA and MNT by OASIS
- Protein binding alerts for CA by OASIS

3. Results and discussion

The aim of this study was to develop a set of structural space alerts to enable the genotoxicity of the α-chloroacetamides group of plant protection products to be predicted via read-across. A series of sub-structures linked to key metabolic transformations were defined based on an expert analysis of the metabolic information available in the DAR documents for the α-chloroacetamides group of plant protection products. The resulting structural space alerts extends the previously published work (Enoch et al., 2023), enabling chemical categories to be developed in which analogues undergo a common set of metabolic transformations. Importantly, these structural space alerts enable chemical categories to be developed for chemicals that lack specific structural alerts for genotoxicity. The ability to group such compounds based on metabolic similarity increases the robustness, reliability, and repeatability of the resulting read-across predictions.

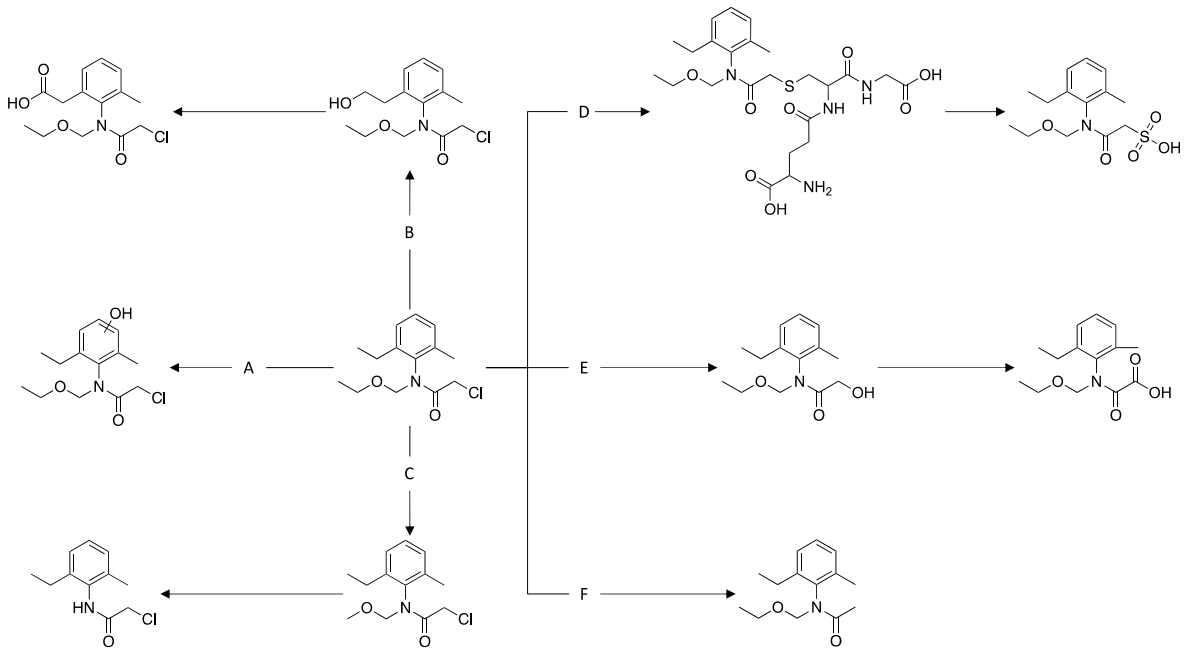


Fig. 1. Summary of the common metabolic pathways present in the α-chloroacetamide class of pesticides (exemplified with acetochlor).

Table 1
Structural space alerts defined for the α-chloroacetamide class of herbicides based on the metabolic map shown in Fig. 1 (R groups as defined, X represents the primary atom/atoms at which metabolism defined in Fig. 1 occurs, no alert is defined for the styrene scaffold in alert set 2 as there are no compounds in the dataset for this area of chemical space).

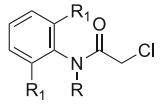
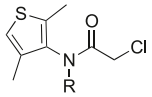
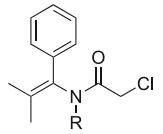
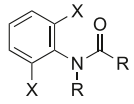
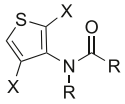
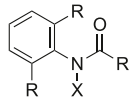
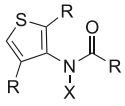
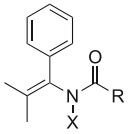
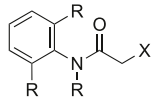
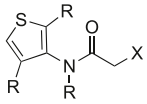
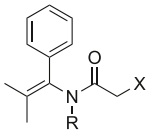
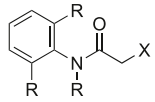
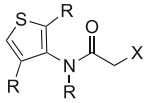
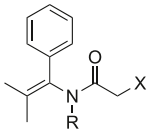
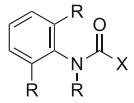
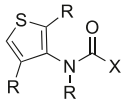
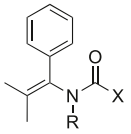
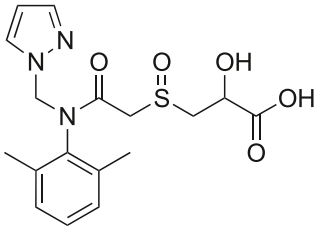
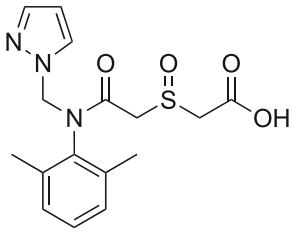
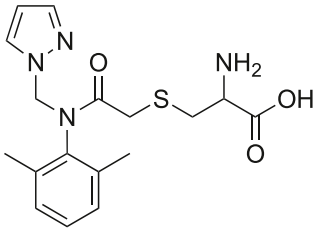
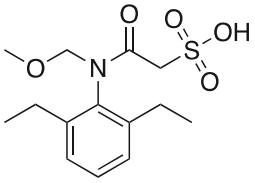
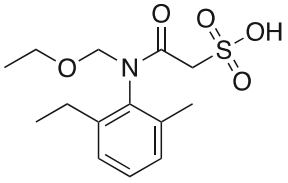
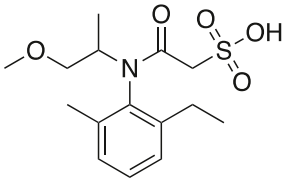
Alert set	Structural space alert			Substituents	Key pathway (Related to metabolism at X)
	Benzene scaffold	Thiophene scaffold	Styrene scaffold		
1				R = any atom R_1=H, CH_2, CH_3	Parent
2			No alert	R = any atom X = CH_2, CH_3	Ortho-oxidation (Pathway B) (Minor metabolic pathway)
3				R = any atom X = CH_2OCH_2, CH_2OCH_3	Dealkylation (Pathway C) (Minor metabolic pathway)
4				R = any atom X = any sulphur	Glutathione conjugation (Pathway D) (Major metabolic pathway)
5				R = any atom X = any oxygen	Hydrolysis (Pathway E) (Major metabolic pathway)
6				R = any atom X = CH_3	De-halogenation (Pathway F) (Minor metabolic pathway)

Table 2
Structural space alert profiling of compound 479M16 leading to the chemical category formed for compound as a result of profiling using the structural space alerts defined in Table 1 (chemical ID for the Target taken from the metazachlor DAR document, analogues IDs as listed in the supplementary information, all genotoxicity data are experimental, except those prefixed with R/A which are read-across predictions).

ID	Structure	Structural space alert (Metabolic pathway)	Genotoxicity data
479M16 (Target)		Alert set 2 - benzene (Ortho-oxidation) Alert set 4 - benzene (Glutathione conjugation)	R/A: Ames (-ve) R/A: *In vitro* CA (-ve) R/A: *In vivo* MNT (-ve)
HRAC-15-15		Alert set 2 - benzene (Ortho-oxidation) Alert set 4 - benzene (Glutathione conjugation)	Ames (-ve) *In vivo* MNT (-ve)
HRAC-15-20		Alert set 2 - benzene (Ortho-oxidation) Alert set 4 - benzene (Glutathione conjugation)	Ames (-ve) *In vivo* MNT (-ve)
HRAC-15-25		Alert set 2 - benzene (Ortho-oxidation) Alert set 3 - benzene (Dealkylation) Alert set 4 - benzene (Glutathione conjugation)	Ames (-ve) *In vitro* CA (-ve) *In vivo* MNT (-ve)
HRAC-15-32		Alert set 2 - benzene (Ortho-oxidation) Alert set 3 - benzene (Dealkylation) Alert set 4 - benzene (Glutathione conjugation)	Ames (-ve) *In vitro* CA (-ve) *In vivo* MNT (-ve)
HRAC-15-43		Alert set 2 - benzene (Ortho-oxidation) Alert set 3 - benzene (Dealkylation) Alert set 4 - benzene (Glutathione conjugation)	Ames (-ve) *In vitro* CA (-ve) *In vivo* MNT (-ve)

3.1. Metabolic map development

The parent compounds of the α-chloroacetamide group of herbicides consist of a single common scaffold featuring the key (to biological activity) α-chloroacetamide moiety along with two R-group substituents. Analysis of the rat metabolism data in the publicly available DAR documents showed the parent structures to undergo six key metabolic transformations (summarised in Fig. 1).

A. Aromatic hydroxylation (minor metabolic pathway): the presence of a benzene ring in the R_1 position enables hydroxylation reactions to occur on this moiety. These are commonly placed in the *para*-position; however, the experimental data does not rule out hydroxylation at other, unsubstituted, ring positions. Replacement of the benzene ring with a thiophene prevents this type of reaction occurring (with, instead, the sulphur of the thiophene undergoing oxidation).
B. Aliphatic hydroxylation (minor metabolic pathway): the presence of methyl or ethyl groups in the *ortho*-positions of the benzene (or thiophene) substituent at R_1 enables hydroxylation reactions to

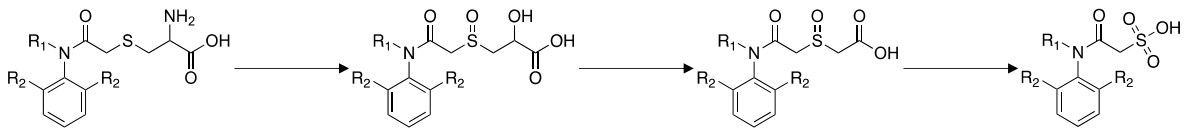


Fig. 2. Metabolic relationships between the category members outlined in Table 2 (R_1 = alkyl ether or ethyl pyrazole; R_2 = methyl or ethyl).

occur resulting in the production of primary and secondary aliphatic alcohol moieties (depending on whether the *ortho*-substituent is methyl or ethyl). The primary aliphatic alcohols can then undergo further oxidation to carboxylic acids. The absence of *ortho*-substituents on the benzene ring prevents this type of metabolism.

C. Dealkylation (minor metabolic pathway): most of the compounds feature an alkyl chain terminated by an ether group. These aliphatic chains undergo a series of dealkylation steps that ultimately remove the alkyl chain at this position, replacing it with a hydrogen. However, the presence of an aromatic moiety in the terminal position (typically a pyrazole ring) prevents this metabolism.
D. Glutathione conjugation (major metabolic pathway): the α-chloroacetamide moiety undergoes glutathione conjugation reactions which, ultimately, produce compounds in which the chloro group is replaced with a sulphate moiety via a series of chain shortening reactions.
E. Hydrolysis/oxidation (major metabolic pathway): the α-chloroacetamide moiety also undergoes a hydrolysis reaction in which the chloro group is replaced by hydroxyl. The resulting alcohol moiety is then further oxidised into a carboxylic acid, resulting in a dicarbonyl species. The hydrolysis/oxidation pathway is in competition with the glutathione conjugation pathway outlined in D.
F. De-halogenation (minor metabolic pathway): the final reaction of the α-chloroacetamide involves glutathione-mediated de-halogenation of the chloro group. This reaction results in a ketone.

3.2. Structural space alert development

The metabolic map outlined in Fig. 1 was used to develop a set of six sets of structural space alerts enabling compounds to be grouped into metabolically related categories (in keeping with previous work in this area (Enoch et al., 2022a; Enoch et al., 2023; Enoch et al., 2022b)). These alerts are as shown in Table 1 and relate to three key scaffolds in the dataset, benzene, thiophene and styrene (where the X group represents the metabolic pathway defined in Fig. 1 that the alert is related to, no alert was defined in alert set two for the styrene scaffold as there were no compounds in this area of chemical space in the dataset). The structural space alerts relate to five of the six pathways defined in Fig. 1, these being: whether the chloro-moiety has undergone metabolism or not i.e., the parent in which the chloro group is still present (alert set 1 in Table 1), oxidation of an alkyl moiety in the ortho-position of the aromatic ring (pathway B in Fig. 1, alert set 2), dealkylation of the ether containing alkyl chain substituent (pathway C, alert set 3), glutathione conjugation at the α-chloroacetamide moiety (pathway D, alert set 4), hydrolysis/oxidation at the same group (pathway E, alert set 5) and the de-halogenation of the α-chloroacetamide group (pathway F, alert set 6). Finally, the differentiation in scaffolds (benzene, thiophene and styrene) accounts for pathway A. This is because this pathway applies to scaffold containing a benzene rings, with then presence of a thiophene ring resulting in the oxidation of the sulphur instead of hydrolysis on the ring.

3.3. Structure-toxicity relationship

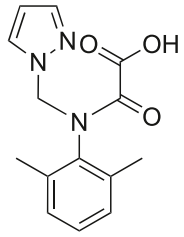
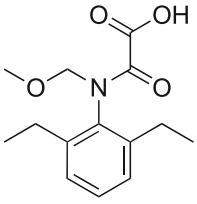
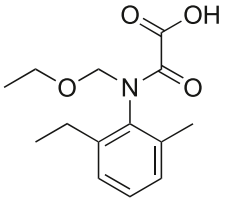
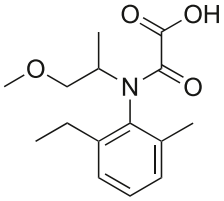
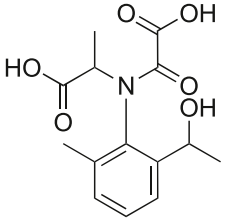
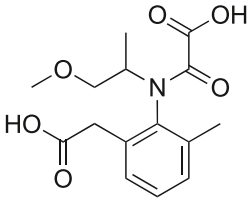
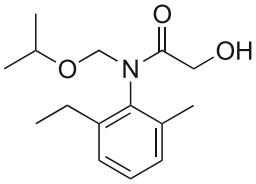
The structural space alerts outlined in Table 1 can be used as the basis for a structure-toxicity relationship analysis allowing the effect of metabolism at each substituent upon genotoxicity to be investigated. Inspection of the data showed that all 69 compounds tested negative in the Ames test (in the standard battery, including with S9). However, 16 of these compounds tested positive in an *in vitro* CA assay (with a further compound being equivocal). It is worth noting that all 17 of these compounds tested negative in an *in vivo* MNT assay. Closer inspection of the chemical structures of these compounds showed four being parent structures containing the reactive α-chloroacetamide moiety (which would fall under alert set 1 in Table 1), with a further eight containing a carboxylic acid group added via metabolism (as part of pathways B, D or E in Fig. 1, alert sets 2, 4 and 5 respectively). However, none of these groups are overly predictive of a positive result in the *in vitro* CA assay as the remaining six parent structures, and a further 17 carboxylic acid containing compounds were all negative (all part of the same alert sets as the positive compounds). All other substituent combinations were negative in the Ames, *in vitro* CA, and *in vivo* MNT assays, making the overall structure-toxicity space negative for genotoxicity. This is in keeping with previous analysis of the sulphonyl urea, triazole, and strobilurins pesticide classes (Enoch et al., 2022a, 2022b, 2023).

3.4. Read-across case study: 479M16

The structural space alerts outlined in Table 1 were used to profile 479M16 a metabolite of metazachlor identified as being a major residue in plants (with a total radioactive residue value of 48% as documented in the DAR for metazachlor). The profiling identified of this compound triggered two structural space alerts (relating to the benzene scaffold in alert sets 2 and 4 in Table 1) related to ortho-oxidation and glutathione conjugation (pathways B and D respectively in Fig. 1. In addition, the presence of a benzene ring within the Target compound indicated the potential for oxidation of this ring system via the addition of a hydroxyl group (pathway A in Fig. 1). Profiling of the α-chloroacetamide dataset resulted in the initial identification of two analogues with the same metabolic profile for which *in vivo* micronucleus data were available (compounds HRAC-15-16 and HRAC-15-20 in Table 2). Importantly, the glutathione pathway is one of the major pathways present within the α-chloroacetamide class. This enabled additional profiling to be carried out to identify related compounds also able to undergo this major route of metabolism. This resulted in the identification of an additional three compounds (HRAC-15-25, HRAC-15-32, and HRAC-15-43 in Table 2). It is worth noting that these compounds do not fully share the metabolic profile of the Target as all three of them can potentially undergo a dealkylation reactions (a minor metabolic pathway as shown by pathway C in Fig. 1, structural space alert set 3 in Table 1). The metabolic relationships between the five analogues are as shown in Fig. 2 - the key steps along the glutathione pathway being the oxidation of amine to hydroxyl, the oxidation of thioether to sulfoxide, and chain shortening reactions involving the cleavage of carboxylic acid groups ultimately resulting in a sulphate moiety.

In keeping with previous work using structural space alerts (Enoch et al., 2022a, 2022b, 2023), the category members were also profiled for their potential ability to react covalently with proteins and DNA using the endpoint specific OASIS profilers within the OECD QSAR Toolbox, the results indicated that an absence of reactive functional groups in the category members. The resulting chemical category is as shown in Table 2, with the available data enabling the Ames test, *in vitro* chromosomal aberration, and *in vivo* micronucleus test assay results to be predicted as negative via read-across for the Target compound.

Table 3
Structural space alert profiling of compound 479M04 leading to the chemical category formed for compound as a result of profiling using the structural space alerts defined in Table 1 (chemical ID for the Target taken from the metazachlor DAR document, analogues IDs as listed in the supplementary information, all genotoxicity data are experimental, except those prefixed with R/A which are read-across predictions).

ID	Structure	Structural space alert (Metabolic pathway)	Genotoxicity data
479M04 (Target)		Alert set 2 - benzene (Ortho-oxidation) Alert set 5 - benzene (Hydrolysis)	R/A: Ames (-ve) R/A: *In vitro* CA (-ve) R/A: *In vivo* MNT (-ve)
HRAC-15-26		Alert set 2 - benzene (Ortho-oxidation) Alert set 3 - benzene (Dealkylation) Alert set 5 - benzene (Hydrolysis)	Ames (-ve) *In vitro* CA (-ve) *In vivo* MNT (-ve)
HRAC-15-29		Alert set 2 - benzene (Ortho-oxidation) Alert set 3 - benzene (Dealkylation) Alert set 5 - benzene (Hydrolysis)	Ames (-ve) *In vitro* CA (-ve) *In vivo* MNT (-ve)
HRAC-15-43		Alert set 2 - benzene (Ortho-oxidation) Alert set 3 - benzene (Dealkylation) Alert set 5 - benzene (Hydrolysis)	Ames (-ve) *In vitro* CA (-ve) *In vivo* MNT (-ve)
HRAC-15-45		Alert set 2 - benzene (Ortho-oxidation) Alert set 3 - benzene (Dealkylation) Alert set 5 - benzene (Hydrolysis)	Ames (-ve) *In vitro* CA (-ve) *In vivo* MNT (-ve)
HRAC-15-48		Alert set 2 - benzene (Ortho-oxidation) Alert set 3 - benzene (Dealkylation) Alert set 5 - benzene (Hydrolysis)	Ames (-ve) *In vitro* CA (+ve) *In vivo* MNT (-ve)
HRAC-15-67		Alert set 2 - benzene (Ortho-oxidation) Alert set 3 - benzene (Dealkylation) Alert set 5 - benzene (Hydrolysis)	Ames (-ve) *In vitro* CA (+ve) *In vivo* MNT (-ve)

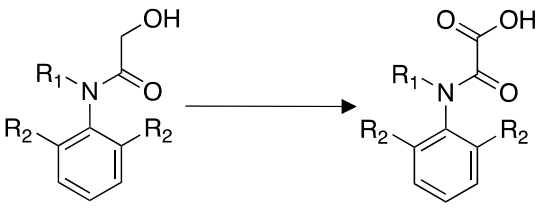


Fig. 3. Metabolic relationships between the category members outlined in Table 3 (R_1 = alkyl ether or ethyl pyrazole; R_2 = methyl or ethyl).

3.5. Read-across case study: 479M04

The structural space alerts outlined in Table 1 were also used to profile a second metabolite of metazachlor, 479M04. This compound having been identified as also being a major residue in plants (with a total radioactive residue value of 28% as documented in the DAR for metazachlor). This profiling triggered two structural alerts relating to ortho-oxidation and hydrolysis within the benzene scaffold (alert sets 2 and 5 in Table 1). Initial profiling for analogues within the α-chloroacetamide dataset containing both alerts failed to identify any compounds with *in vivo* data (only a single compound with an Ames test result was identified). An additional search for analogues was carried out for compounds capable of undergoing the hydrolysis pathway, as this was the major metabolic pathway identified in the Target chemical. This resulted in the identification of six analogues featuring the benzene scaffold, none of which triggered any alerts for DNA reactivity (profiling schemes as per the first case study for compound 479M16). These six compounds were used to predict the genotoxicity of the Target chemical, 479M04, as negative. Chemical and toxicological data as shown in Table 3, with metabolic relationship between the analogues for the hydrolysis pathway as shown in Fig. 3.

4. Conclusions

This study has further developed the structural space alert concept extending it to cover the α-chloroacetamide herbicides. The results showed outlined how structural space alerts could be explicitly linked to key metabolic transformations for this class of compounds, and how these alerts could be used to identify metabolically similar analogues to fill genotoxicity data-gaps via read-across, with a focus on the *in vivo* micronucleus test. Importantly, the case studies outlined how analogues could be identified based on either a common set of metabolic transformations or with a focus on the major metabolic pathway within the Target chemical. The inclusion of information around the relative importance of the pathways covered by the structural space alerts being an expansion of the concept. In keeping with previous work in this area, the proposed workflow does rely on the availability of metabolic data (typically from DAR/RAR documents) and expert judgement around the key site (or sites) of metabolism upon which to focus the development of the metabolic maps. In addition, it is possible that metabolites may fall out of the scope of the defined structural space alerts. To this end, the EFSA's ongoing efforts to make ADME data available for pesticide compound classes is a welcome development (zenodo.org/doi/10.5281/zenodo.4601173). At the time of writing research is ongoing to expand the approach to other pesticide compound classes and implementation of a metabolic similarity profiling scheme within the OECD QSAR Toolbox.

Funding body

Crop Life Europe are gratefully acknowledged for funding this research.

CRediT authorship contribution statement

S.J. Enoch: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Z. Hasarova:** Writing - review & editing, Formal analysis, Data curation, Conceptualization. **M.T.D. Cronin:** Writing – review & editing, Funding acquisition. **K. Bridgwood:** Writing – review & editing. **S. Rao:** Writing – review & editing. **F.M. Kluxen:** Writing – review & editing. **M. Frericks:** Writing – review & editing, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Zuzana Hasarova reports financial support was provided by Crop Life Europe.

Data availability

All data are in the SI

Acknowledgements

This research received funding from CropLife Europe.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yrtph.2024.105641.

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