molecules that attack and destroy lipids and protein membranes. When a lipid membrane is destroyed, cell becomes leaky and cell organelles dry and disintegrate rapidly [84].

PPO inhibitors have limited translocation in plants and sometimes are referred to as contact herbicides. PPO inhibitors injure mostly broadleaf plants; however, certain PPO inhibitors have some activity on grasses. PPO inhibitors usually burn plant tissues within hours or days of exposure. PPO inhibitors used in the United States belong to eight different chemistries including diphenyl ethers, *N*-phenylphthalimides, oxadiazoles, oxazolidinediones, phenylpyrazoles, pyrimidinediones, thiadiazoles, and triazolinones. These herbicides are used to control weeds in field crops, vegetables, tree fruits and vines, small fruits, nurseries, lawns, and industry. Recent works have shown the evolution of different mutations, ΔG210, Arg98Gly, Arg98Met, and Arg98Leu in *A. tuberculatus*, *A. palmeri*, and *Ambrosia artemisiifolia* [85–87].

#### 1.3.3.2 Nontarget-site Resistance (NTSR) by Enhanced Metabolic Detoxification

Plants dispose of enzyme systems that catalyzethe metabolic conversion of xenobiotic, including herbicides. The metabolites that usually are more polar than the parent compound are either nonphytotoxic at all or have a reduced phytotoxicity. Among the various enzyme systems involved in metabolic herbicide detoxification, two are of particular importance in weeds and crops:

- *The cytochrome P450 monooxygenase system*: This system (several protein families) catalyzes oxidative transformations of the herbicide molecule (e.g. hydroxylations and oxidative dealkylations). In fact, the system is a member of a large enzyme family that consists of multiple cytochrome P450 monooxygenases with diverse substrate specificities [88].
- *Glutathione S-transferase (GST, EC 2.5.1.18):* This family of enzymes catalyzes conjugation reactions that result in the nucleophilic displacement of aryloxy moieties, chlorine, or other substituents by the tripeptide glutathione (GSH). The GSTs also occur in various isoforms that differ in their catalytic properties [89].

The herbicide tolerance of crop species has been found to be based frequently on differential rates of metabolic herbicide detoxification in crop and weed species. While the rates of herbicide detoxification among weed species are too low to prevent the binding of a lethal herbicide dosage at the target site, the tolerant crop is able metabolically to detoxify the herbicide at such a high rate that binding of the herbicide to its target site in sufficient amounts to cause irreversible herbicidal effects will be prevented. If weed biotypes with an improved ability for herbicide detoxification, comparable with the tolerant crop species, occur in a population, they will survive herbicide application and will thus be selected. This enzyme system-based resistance mechanism is no more related to the target of the herbicide (i.e. its site/MoA) but rather to its chemical structure and therefore causes unexpected cross-resistance to herbicides from different chemical classes with different sites/MoA as well to herbicides that have not been so far used.

To date, many populations in several weed species have been described for which HR was related to an enhanced metabolic herbicide detoxification. An early report from Christopher et al. [90] stated that the excised shoots of *L. rigidum* SLR 31 population from Australia, which was resistant to diclofop-methyl-methyl, exhibited a cross-resistance to the SUs chlorsulfuron, metsulfuron-methyl, and triasulfuron. Although the metabolite pattern of chlorsulfuron was identical in the resistant population and a susceptible population, the resistant population metabolized faster the herbicide. The pathway of chlorsulfuron detoxification in *L. rigidum* was similar to that described for wheat with ring hydroxylation being followed by glycosyl conjugation. The time course of chlorsulfuron metabolism in the *L. rigidum* population SR 4/84 (resistant to diclofop-methyl-methyl and cross-resistant to chlorsulfuron) was analyzed separately in shoots and roots. The half-life of chlorsulfuron in susceptible plants was longer in the roots (13 hours) than in the shoots (4 hours) and was reduced in the resistant population to 3 and 1 hours, respectively. Detoxification of the herbicide by ring hydroxylation most likely catalyzed by a cytochrome P450-dependent monooxygenase, with subsequent glucose conjugation, was enhanced in the resistant population [57]. Nevertheless, it is so far not shown at the gene level that the respective Cyt P450 and glycosyltransferase are encoded by homologous genes in both the crops and the weeds.

Two other *L. rigidum* populations from Australia (WLR2 and VLR69) developed metabolism-based resistance to PS II inhibitors. In this case, WLR2 was obtained from a field with selection pressure by atrazine and amitrole, but never by phenylureas, while VLR69 was obtained from a field with selection pressure by diuron and atrazine. Both populations were resistant to triazines and, despite the field selection by atrazine, resistance was more pronounced to the structurally related simazine. Furthermore, both populations were resistant to chlorotoluron, though only VLR69 had previously been exposed to phenylureas. The results of analytical studies revealed that, in both resistant populations, the metabolism of chlorotoluron and simazine was enhanced and that the main route of their metabolism was via N-dealkylation reactions. This type of reaction coupled to the fact that herbicide metabolism was inhibited by 1-aminobenzotriazole (1-ABT), an inhibitor of cytochrome P450 monooxygenases, suggested an increased activity of cytochrome P450 monooxygenases in the resistant populations [91, 92]. The mechanism of phenylurea resistance of *L. rigidum* populations from Spain has been studied [93]. A population (R3) selected in the field by applications of diclofop-methyl-methyl, and isoproturon or chlorotoluron, had *in vivo* resistance factors ($ED_{50}$ R (resistant)/$ED_{50}$ S (susceptible)) of about 9.3 and 5.5 to chlorotoluron and isoproturon, respectively, and was also resistant to a broad spectrum of other phenylureas. Metabolism studies with chlorotoluron in the absence and presence of the cytochrome P450 monooxygenase inhibitor 1-ABT suggested that resistance was due to an enhanced ability to degrade the molecule to nontoxic ring-alkylhydroxylated intermediates suitable for follow-up conjugation reactions. In other studies, several populations of *L. multiflorum* from the United Kingdom with resistance to diclofop-methyl-methyl have been analyzed [39]. While one

population had an insensitive ACCase, the resistance of three other populations could be attributed to an enhanced metabolism of this herbicide.

The resistances of the grass weed *Phalaris minor* to isoproturon, and of the dicotyledonous weed species *Abutilon theophrasti* to atrazine, has also been attributed to an enhanced metabolism. Here, GST was noted as the enzyme responsible for atrazine detoxification in *A. theophrasti* [94], whereas in *P. minor,* the cytochrome P450 monooxygenase was most likely involved in the enhanced detoxification of isoproturon [95].

An increasing occurrence of the resistance of *A. myosuroides* to herbicides in several European countries has prompted investigations into resistance mechanisms in this species. Aside from target-site-based resistance cases, resistance due to an enhanced herbicide metabolism has also been reported. Two populations – Peldon Al and Lincs El – with *in vivo* resistance factors to isoproturon of 28 and 2.6, respectively, were shown to metabolize this herbicide faster than a susceptible reference population with the rate of metabolism being higher in Peldon than in Lincs. The addition of the cytochrome P450 monooxygenase inhibitor 1-ABT lowered the rate of chlorotoluron metabolism and correspondingly increased phytotoxicity; this suggested an involvement of the cytochrome P450 monooxygenase system in the detoxification of the herbicide. However, the major detoxification reaction in these populations appeared to be the formation of a hydroxymethylphenyl metabolite [96].

The same populations, Peldon Al and Lincs El, are also resistant to the graminicide fenoxaprop, which is used for the selective control of *A. myosuroides* and other grassy weeds in cereals (mainly wheat). On a whole-plant level, Lincs El was more resistant than Peldon Al. The selectivity of this herbicide has been attributed to a rapid detoxification via GST-catalyzed conjugation in the cereal species. In both resistant *A. myosuroides* populations, the GST activities toward fenoxaprop were shown to be increased, when compared with a susceptible population. This was due to an increased expression of a constitutive GST and to the expression of two novel GST isoenzymes. Furthermore, GSH levels were increased in the resistant populations, in Peldon more than in Lincs. These data pointed to an involvement of GST activity and GSH levels in the resistance to fenoxaprop, although a lack of correlation to the whole-plant resistance of these populations did not permit definite conclusions to be drawn [97]. Further work overexpressing in *Arabidopsis*, a GST overexpressed in herbicide-multiresistant *A. myosuroides*, Peldon population suggests its involvement in resistance to herbicides [98]. Recently, a range of European *A. myosuroides* populations with resistance to fenoxaprop has been investigated [99], and several of these populations – notably one from Belgium – were shown to detoxify the herbicide at an increased rate. The population from Belgium also had the highest GST activity toward the unspecific substrate chlorodinitrobenzene (CDNB) although GST activity toward the herbicide was not tested.

Studies on the mode of inheritance of metabolic HR in *A. myosuroides* and *L. rigidum* postulated that more than one gene is involved in cytochrome P450 metabolism-based resistance in weed populations [100–102]. Recent works using transcriptome analyses have allowed to make steps forward in the identification

of several genes involved in herbicide detoxification [103–105]. The occurrence of an enhanced metabolic detoxification can be associated with an ecological cost expressed in a reduction of the vegetative biomass and reproduction rate [72]. In contrast to the above-described cases, the herbicide propanil is detoxified in rice and weed species by the action of an aryl acylamidase (aryl-acylamine amidohydrolase). A high activity of this enzyme in rice confers crop tolerance. In Colombia, a population of *Echinochloa colona* resistant to propanil was found; subsequent enzyme tests with extracts from this population revealed an almost threefold higher activity of aryl acylamidase in the resistant than in a susceptible population. Based on these findings, it was concluded that resistance of the *E. colona* population is related to an enhanced propanil detoxification [106].

The HPPD inhibitors in particular the triketone chemistry (e.g. tembotrione and mesotrione) inhibit the oxidative decarboxylation and rearrangement of p-hydroxyphenylpyruvate (HPP) to homogentisate (HGA), which inhibits the catabolism of tyrosine and results in a deficiency of plastoquinone and α-tocopherols (vitamin E) [107]. Recent data suggested that detoxification involving Cyt P450 monooxygenase is involved in mesotrione resistance of *A. palmeri* [108]. Recent development in genomics has brought new insight in the characterization of the genes encoding for the enzymes involved in herbicide detoxification.

This new knowledge could contribute in the next years to find novel solutions to mitigate nontarget-site HR by detoxification.

Today, genomic sequencing [109] allowed to have a faster access of genes encoding detoxification enzymes in order to characterize them as, for example, GSTs involved in Group 15 herbicide detoxification like flufenacet [110, 111] or pyroxasulfone [110].

#### 1.3.3.3 Nontarget-site Resistance by Altered Herbicide Distribution

Cases of nontarget-site resistance by altered herbicide distribution have been reported for two important herbicides, paraquat and glyphosate.

The intensive use of paraquat has resulted in an evolution of resistance in various weed species. Subsequently, intensive investigations into the resistance mechanisms involved were mainly carried out using resistant populations from *Hordeum* spp. and *Conyza* spp., and an altered distribution of the herbicide in the resistant weeds was suggested as the cause – or at least the partial cause – of resistance. In resistant *Conyza canadensis*, it was supposed that a paraquat-inducible protein might function by carrying paraquat to a metabolically inactive compartment, either the cell wall or the vacuole. This sequestration process would prevent sufficient amounts of the herbicide from entering the chloroplasts, which is the cellular site of paraquat action. Inhibitors of membrane transport systems such as *N,N*-dicyclohexylcarbodiimide (DCCD) caused a delay in the recovery of the photosynthetic functions of a paraquat-resistant population when administered after the herbicide. The results of these transport inhibitor experiments supported the involvement of a membrane transporter in paraquat resistance [112].

Translocation studies with two paraquat-resistant populations of *Hordeum leporinum* revealed that the basipetal transport of paraquat was much reduced compared

with susceptible plants. It was concluded therefore that a resistance to paraquat was the result of a reduced herbicide translocation out of the treated leaves [113]. It might be supposed that, also in this species, herbicide sequestration into the leaf vacuoles may have been the primary cause for the altered long-distance transport [114].

The high efficiency of glyphosate as a potent herbicide is based on its ability to translocate within the plant via xylem and phloem to the apical and root meristems as well as to the reproductive organs of perennial plants. Independent populations of *L. rigidum* with resistance to glyphosate have been reported from different locations in Australia. One of these, with an approximately 10-fold *in vivo* resistance to glyphosate, was used to conduct intensive investigations into the mechanism of resistance. Neither a modification of the target enzyme EPSPS nor a herbicide metabolism contributed to the resistance in this case. However, translocation studies following foliar application revealed that in the resistant population, glyphosate accumulated preferentially in the leaf tips, whereas in susceptible plants, the accumulation was greater in the leaf bases and roots. These results suggested a shift of glyphosate transport in the resistant plants from the phloem to the xylem system. Thus, it was speculated that the resistant population might have lost an efficiency to load glyphosate into the symplast, such that more of the herbicide would remain in the apoplast and be translocated acropetally with the transpiration stream. Consequently, the concentration of glyphosate in the plastids of the sensitive meristematic tissues at the shoot base and in the roots would be reduced [115]. Meanwhile, a reduced glyphosate translocation within the plants and to the roots was confirmed for different *C. canadensis* and *L. rigidum* populations from different countries (for reviews, see Refs. [77, 116]). It was speculated that the membrane transporters were responsible for pumping the herbicide either into vacuoles or out of the chloroplast, such that the herbicide was unable to reach the target site [116].

Plants can develop resistance to synthetic auxin herbicides like 2,4-D or dicamba via transport inhibitor mechanisms or metabolism or other mechanisms as reviewed [117]. Recent data suggest that transport inhibition plays an important role of resistance of *Papaver rhoeas* to 2,4-D [118].

#### 1.3.3.4 Multiple Resistance

As defined above, multiple resistance means that more than one resistance mechanism occurs in a weed population or an individual plant. This can either mean that both target-site-based and nontarget-site-based mechanisms occur in the same population or that a population is resistant to herbicides with different mechanisms of action. Multiple resistance can result in the resistance of a weed population to a very broad range of herbicide chemistries. Multiple resistance has been reported for several weed species (Figure 1.6), notably *L. rigidum*, *A. myosuroides*, *K. scoparia*, *D. insularis*, *C. canadensis*, *A. palmeri*, and *A. tuberculatus* (http://weedscience.org/). Such multiple resistance developed to a major extent especially in the Australian populations of *L. rigidum* most likely as a result of agricultural conditions paired with biological characteristics of this weed (cross-pollinating species with a high genetic variability and seed production and high plant numbers per area). Similarly, *Amaranthus* spp. have evolved multiple resistance in the simplified agronomic

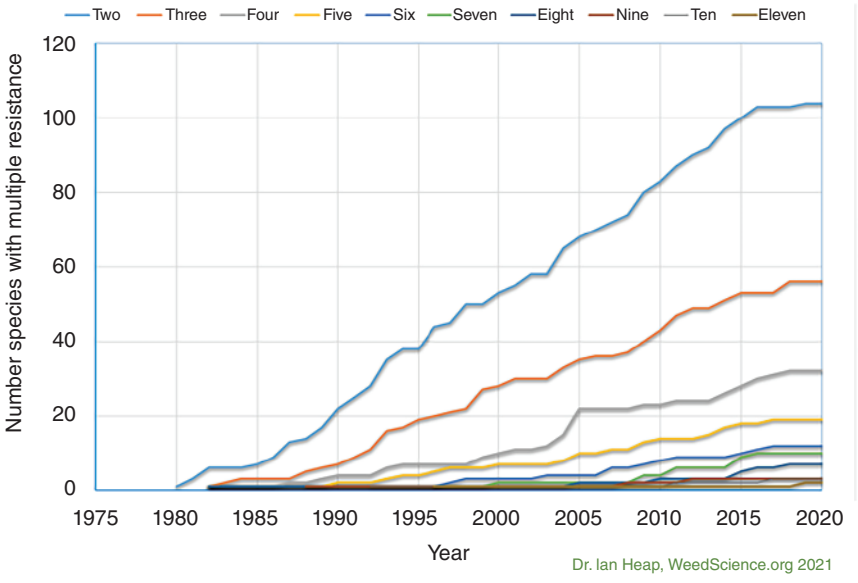


**Figure 1.6** The recent chronological evolution of species for which populations showing resistance to multiple sites/modes of action. *Source:* Reproduced with permission of Heap 2024 [4].

practices used in the United States, and the same trend can be observed in South America (soybean and maize crops) and in grasses in Europe (cereal-based cropping systems).

Multiple resistance can develop by selection with a single herbicide or several herbicides that are used either sequentially or simultaneously. Moreover, cross-pollinating species may become multiple resistant when two individuals, each with a different resistance mechanism, undergo hybridization. An example of the selection of multiple resistance by a single herbicide (the ALS inhibitor chlorsulfuron) is the *L. rigidum* population WLRl. As the main mechanism of resistance, this population had an ALS with reduced sensitivity to chlorsulfuron, sulfometuron, and imazethabenz and, as additional mechanism, an enhanced metabolism of chlorsulfuron [119]. Extreme cases of multiple resistance, due to an application history of many herbicides, were reported from Australia for several *L. rigidum* populations. For example, population VLR69 possessed the following mechanisms: an enhanced metabolism of ACCase-inhibiting herbicides, a resistant form of the ACCase enzyme, an enhanced metabolism of the ALS inhibitor chlorsulfuron, and also a resistant form of the ALS enzyme in 5% of the population [41].

The selection of multiple resistance following the sequential use of different herbicides has been described for a population of *K. scoparia* from North America. In this case, many years of triazine usage resulted in the selection of a population with target-site resistance of the Dl protein in PS II. Following the subsequent use of ALS inhibitors, a point mutation in the gene encoding for ALS was selected in addition, which made this population target site resistant also to SUs and IMIs [67].

Some *Lolium* populations from Australia and South Africa have shown both target site and a reduced translocation to glyphosate [77]. Further examples of weed species and populations with multiple resistance mechanisms have been described in various reviews and also in the database of the International Survey of Herbicide-Resistant Weeds [4, 120]. Clearly, multiple resistance leads to complex patterns of broad HR, particularly in cross-pollinating weed species. This can cause a serious restriction on the remaining options for chemical weed control in agricultural practice.

### 1.3.4 Global Herbicide Resistance Action Committee (HRAC)

#### 1.3.4.1 Missions and Goals

The Global HRAC (http://hracglobal.com/who-we-are/about) is an international body founded by the agrochemical industry, which helps to protect crop yields and quality worldwide by supporting efforts in the fight against herbicide-resistant weeds.

Herbicides are the primary economic means to control weeds, and they play a crucial role in helping humanity feed itself. The evolution of herbicide-resistant weeds is a serious problem facing the global agricultural community – they threaten the regions, economies, and livelihoods of farming families. But HR can be managed, and HRAC provides the information necessary to take a stand against herbicide-resistant weeds.

HRAC is dedicated to a cooperative approach to the management of herbicide-resistant weeds. By collecting, assessing, and sharing information on weed resistance, HRAC acts as a comprehensive and reliable source for the people who feed our growing world. The work done by the Global HRAC contributes to sustainable crop practices worldwide, which allow farming families to grow more food on less land and help preserve and protect our natural resources, in particular soils, for generations to come.

From rural communities to agriculture experts, HRAC provides the knowledge to protect the planet while winning the fight against HR.

#### 1.3.4.2 Members, Organization, and Tasks

The Global HRAC is an industry-based group administrated by CropLife International (CLI, https://croplife.org/). The organization is operated by important members of the agrochemical industry:

- CLI Members
- BASF
- Bayer CropScience
- Corteva Agriscience
- FMC
- Syngenta Crop Protection
- Sumitomo Chemical Company
- Non CLI Members.
- Gowan
- UPL

The Global HRAC supports the work of regional offices around the world. Global HRAC equips them with the resources they need to bring education on herbicide-resistant weeds to farmers, agronomists, industry members, and officials. Global HRAC also identifies and organizes working groups that tackle key HR challenges.

HRAC is supporting the International Survey of Herbicide-Resistant Weeds (http://weedscience.org/) and has set and is updating the Global Classification of Herbicides as described previously. In addition, HRAC has developed several new communication tools summarizing its activities like small videos on MoA classification or IWM management (https://www.hracglobal.com/). In addition, an App was developed and can be uploaded to have a fast access on the MoA classification and information on chemicals (https://www.hracglobal.com/) (Figure 1.7).

Working groups are dedicated to provide comprehensive information on HR and management on particular topics (e.g. synthetic auxins, Group 15 herbicides, HPPD inhibitors) in order to propose the best strategies to mitigate the evolution of resistance. In addition, HRAC is working on the development of information on labels, so growers have the resources they need to make responsible herbicide decisions on their farms. In particular HRAC is proposing to any herbicide registrant to include the site/MoA numbers and guidelines in herbicide labels in the United States and other countries as appropriate. Moreover HRAC is recommending to follow best weed management practices as edited (http://hracglobal.com/files/Management-of-Herbicide-Resistance.pdf). Finally HRAC is working to develop and propose weed resistance mitigation strategies as well as resistance survey and diagnostics (http://hracglobal.com/files/Monitoring-and-Mitigation-of-Herbicide-Resistance.pdf).

HR is evolving because of economic pressure (simplified agronomic systems), higher regulation standards (less herbicides and sites/MoA registered), and less innovation reaching the market. In that context, Global HRAC has the task to become a reference body related to weed control and HR management and is working with all stakeholders (farmers, retailors, advisors, authorities, academics)


**Figure 1.7** App related to the description of the herbicide active ingredients and their respective mode of action. The app also allows to search for fungicides and insecticides.

to promote IWM and maintain the maximum numbers of tools in the tool box to keep the highest diversity to manage weed in a sustainable way. One of the biggest challenge during the next year will be to find novel solutions to mitigate the evolution of non-target-site resistance, in particular herbicide detoxification by populations of the different driving weed species.

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