Technical Bulletin No. 26

A Scientific Appraisal on Herbicides Proposed for Ban/Restriction in India

Shobha Sondhia

J.S. Mishra

ICAR–DIRECTORATE OF WEED RESEARCH

Jabalpur (Madhya Pradesh)

ISO 9001 : 2015 Certified

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Foreword

Weeds pose a significant threat to agriculture and biodiversity because of their innate competitive nature and capacity to consume more resources than crop plants, often resulting in an average global yield loss of almost 37%. The challenges associated with the unavailability and high cost of labour for manual weeding have necessitated the adoption of chemical weed control methods. Herbicides offer a timely and cost-effective solution for managing weeds. In India, there has been a noticeable increase in the use of herbicides over the last two decades both in agricultural and non-agricultural lands. However, the frequent and intensive application of herbicides has led to the development of resistance among weed populations

The Government of India, aware of the potential adverse effects of certain herbicides on human health, non-target organisms, and the environment, regularly reviews and, if necessary, restricts or bans the use of these chemicals, as well as other types of pesticides. Recently, eight herbicides, including 2, 4-D, atrazine, butachlor, diuron, glyphosate, oxyfluorfen, pendimethalin, and sulfosulfuron, were scrutinized from a list of 27 pesticides. The aim is to regulate their usage and mitigate any negative impacts that may arise from their application.

I am pleased to acknowledge the efforts of the ICAR-Directorate of Weed Research, Jabalpur, in publishing a comprehensive review titled, 'A Scientific Appraisal on Herbicides Proposed for Ban/Restriction in India'. This publication commendably compiles a vast array of scientific data on the efficacy and toxicity of the listed herbicides, making it accessible and understandable. I am confident that this document will serve as a valuable resource for policymakers and stakeholders, guiding informed decisions in the management and regulation of herbicide use.

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Preface

The average yield losses caused by the weeds is predicted to be one third among total yield losses caused by various group of pest in the world. With growing labour shortage and increasing cost of manual weeding, herbicides are now becoming increasingly popular because of their cost-efficiency, and timely weed management. In India, use of herbicides is popularized after Green Revolution and exponential growth of herbicide is witnessed in the last two decades especially in case of glyphosate, 2,4-D, atrazine and pendimethalin. Uses of herbicides is further geared up to deal with emerging challenges and threats posed by the weeds in diverse situations that further aggravated by the emerging climate change and development of herbicide resistance in weeds.

Herbicides being synthetic chemicals are specially design to kill weeds and are hazardous with multiple chronic toxic effects, if taken accidently or intentionally. Hence, increasing demand and higher consumption of herbicides every year also become the matter of concern especially due to associated risk on environment, health hazards, and safety concerns. Few herbicides, namely, 2,4-D, atrazine, butachlor, diuron, glyphosate, oxyfluorfen, pendimethalin and sulfosulfuron are put under the scrutiny by the Central Insecticidal Board and Pesticide Registration Committee, Government in India for their bio-efficacy, toxicological data or alternate herbicides in place of these selected herbicides.

Hence a comprehensive document entitled, 'A Scientific Appraisal on Herbicides Proposed for Ban/Restriction in India' has been prepared based on published scientific data at national and global levels to give an overall picture of each herbicide with relevant data which can be helpful to the policy makers, and other stakeholders.

Due to heterogeneity of scientific information in some toxicological studies, the authors do not endorse any adverse or supporting data of any herbicide presented in this bulletin. We hope that this will also serve as a reference material for the Pesticide Registration Committee and other stakeholders.

We welcome all relevant suggestions and comments on this technical bulletin from various readers.

Dated : April, 2024
Place : Jabalpur

Shobha Sondhia
J.S. Mishra

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Disclaimer:
Herbicides being synthetic chemicals are specially design to kill plants/ weeds and are hazardous chemicals with multiple, severe and even fatal, acute as well as chronic toxic effects, if taken intentionally. It has also been found thatmany published studies presented in this bulletin present a great heterogeneity in their results, and in some toxicological studies, the effects of higher doses than the concentrations to which the general population is routinely exposed is reported. Thereforeauthors of this bulletin do not endorse any adverse or supporting data of any herbicide presented in this bulletin.

1. Introduction

Pesticides are being used frequently in the world to manage various pests and diseases. In 2013, about 5.16×10^6 t of pesticides were used worldwide whereas in 2021, 5.48×10^6 t of pesticides were applied globally (FAO 2021). Though pesticides are specifically designed for control of various pests and diseases, however besides their targeted function, their residues remain active and can drift far beyond their target areas *via* air, water, soil erosion or leaching (Sondhia 2014 a,b).

Table 1. Consumption of various pesticides in the world and India (Source FAO, 2021,https://www.fao.org/faostat/en/#data/RP)

Pesticide	World		India	
	2021 (t)	% share	2021(t)	% share
Insecticide	822857	15.02	31731	51.42
Herbicides	1831139	33.42	9749	15.80
Fungicide	1702672	31.08	20092	32.56
Other	1121910	20.48	1130	0.162
Total Pesticide	5478580	100	61702	100

Among various class of pesticides, globally herbicides consumption in agriculture has increased from $1.72x \times 10^6$ t to 1.83×10^6 t in last 10 years (FAO 2023) **(Table 1)**. Studies have shown adverse effect of herbicides on non-target organisms including crop species, microorganisms and invertebrates (Sondhia 2014, Wood et al. 2016, Schreiner et al. 2016) along with negative consequences on the overall biodiversity in various ecosystems (Van Wijngaarden and Arts 2018). Although herbicides are designed to target weeds, but several direct and indirect risk (Brühl and Zaller 2021) as well as lethal and sublethal effects have been reported for non-target organisms such as honey bees, earthworms and birds (Gill et al. 2018, Zaller et al. 2021), etc.

Some herbicides are reported to be associated with both, acute and delayed health effects in exposed humans, ranging from simple skin and eye irritation to more severe impacts on the nervous and the reproductive disorders, neurological dysfunction, cancer and respiratory disorders (Rani et al. 2021). Especially occupational exposure to herbicides is reported to be associated with the development of a wide spectrum of pathologies (Gangemi et al. 2016) such as Parkinson's disease among winemakers (Tangamornsuksan et al. 2019) myocardial infarction among female farmers (Sekhotha et al. 2016) and cardiovascular diseases among farm workers (Ahmad et al. 2021). In addition, occupational and indirect herbicide exposure *via* air drift, water and nutrition was reported to increase the general risk of cancer and other diseases (Brouwer et al. 2017, Kachuri et al. 2017). Exposure to a variety of different herbicide might also trigger synergistic effects (Laetz et al. 2009). Children are more likely to be affected by the exposure of herbicides especially *via* spray drift even at low-dose (Sapcanin et al. 2016). Several countries have restricted /banned various herbicides time to time based on the adverse effects.

As on July, 2023, a total of 299 pesticides were registered in India that includes insecticide, herbicides and fungicides. In viewof proposed restriction/ban of eight herbicides, namely, 2,4-D, atrazine, butachlor, diuron, glyphosate, oxyfluorfen, pendimethalin, sulfosulfurondue to environmental and health concerns, this bulletin aims to assess (i) consumption pattern and uses of these herbicides in various crops, (ii) associated environmental and health risk due to their applications/exposure in agricultural crops, (iii) presence of residues based on various scientific published data from various sources (mostly 2010 to present) as well as (iv) toxicity information on animal and other organisms. Information provided in this bulletin is based on mostly *in vitro* and *in vivo* studies conducted to verify the toxicity induced by listed herbicides and their metabolites in various experimental models (Martins-Gomes et al. 2022).

2. Proposed restriction/ban list of herbicide in India

In India total consumption of chemical based pesticides is approximately 21837 MT in 2023 which represents 0.317 kg/ha pesticide consumption per hectare **(Table 2)**. Among various pesticides used in India, insecticides contribute the highest share.

Table 2. State-wise per ha (kg) consumption of pesticides (technical grade) as on 13 July 2023 in major pesticides consumption states in India (Cultivation Area Source*Cropping Intensity Jan 2021.pdf (nfsm.gov.in)

State	Per ha (kg) pesticide consumption				
	2018-19	2019-20	2020-21	2021-22	2022-23
Andhra Pradesh	0.224	0.207	0.207	0.234	0.266
Assam	0.063	0.101	0.103	0.117	0.112
Bihar	0.112	0.112	0.131	0.112	0.131
Chhattisgarh	0.314	0.296	0.291	0.309	0.315
Goa	0.159	0.191	0.191	0.204	0.217
Gujarat	0.140	0.155	0.137	0.162	0.152
Haryana	0.617	0.645	0.622	0.625	0.625
Karnataka	0.127	0.131	0.161	0.185	0.139
Maharashtra	0.501	0.545	0.564	0.561	0.290
Madhya Pradesh	0.023	0.023	0.029	0.028	0.025
Orissa	0.335	0.232	0.241	0.258	0.281
Punjab	0.704	0.635	0.660	0.683	0.652
Rajasthan	0.092	0.083	0.093	0.084	0.075
Tamil Nadu	0.313	0.366	0.302	0.305	0.321
Telangana	1.000	1.004	1.019	1.006	1.006
Uttar Pradesh	0.422	0.466	0.441	0.446	0.451
West Bengal	0.323	0.367	0.367	0.367	0.336
Average	**0.322**	**0.327**	**0.327**	**0.334**	**0.317**

It is worth to mention that for any herbicide to be used in India, the Central Insecticide Board & Registration Committee (CIB and RC) is empowered to register them for their use in the country and takes references from various international and national documents including International Code of Conduct on Pesticides Management. Registered herbicides are reviewed time to time with regard to their safety and efficacy based on the receipt of new studies / reports/ references/ information by the government. The Registration Committee constituted under section (5) of the Insecticides Act, 1968 while registering the herbicides for use in the country evaluates their safety and bioefficacy based on the field trials conducted at State Agriculture Universities/ICAR institutes and lab studies conducted at NABL /ISO:17025/ and GLP accredited laboratories. For any herbicide to be used in India the Registration Committee approves the details of doses, crops, precautionary measures, antidotes, etc. on Label and Leaflets.

After recommendations by several expert committees, a draft notification was issued on May 2022 to restrict / ban 27 pesticides by the Govt. of India. Among a list of

27 pesticides proposed for restriction/ban, 8 were herbicides which were proposed to be banned by Dr. Anupam Verma committee since 2015. It is noteworthy to mention that Verma committee reviewed 66 pesticides which are banned/restricted in other countries but continued to be register for use in India. Dr Verma committee report was forwarded to the Registration Committee (RC) under section 27(2) of the Insecticides Act, 1968. The Registration committee accepted its recommendations in its 361st special meeting held on December 22, 2015 and, the Government of India, after considering the recommendations of the Expert committee along with observations of the Registration committee, had issued an order on October 14, 2016 whereby out of 66 pesticides, 12 pesticides were banned, 6 pesticides were recommended to be phased out by the year 2020. Dr, S.K. Malhotra Committee reinstated the need to ban 27 pesticides in 2018. Khurana Committee (2020) also suggested ban of same 27 pesticides in India as given by the Committee.

Among 27 pesticides proposed to be banned/restricted, eight are herbicides, namely, 2, 4-D, atrazine, butachlor, diuron, glyphosate, oxyfluorfen, pendimethalin, sulfosulfuron (**Table 3**) and **table 4** showed the status of herbicides restricted for use in the country. Generally it is assumed that the registered herbicides if used as per Label and Leaflets do not pose any harm to human, animals and other living organisms and environment. As on July 2023, 05 herbicides formulations' are banned for manufacture, import and use in the country and 02 herbicides were withdrawn and 02 herbicides are restricted for use (https://ppqs.gov.in/ sites / default / files/10._list_of_ pesticides_which_are_banned_refused_Registration_and_restricted_in_use.pdf assessed on November 2023).

Table 3. Herbicide / formulations banned in India as on 01.06.2023

Herbicides Banned for manufacture, import and use.	Herbicides Withdrawn
Alachlor (Vide S.O. 3951(E), dated 08.08.2018)	Dalapon
Linuron (vide S.O 3951(E) dated 8th August, 2018)	Simazine
Metoxuron	
Nitrofen	
Paraquat Dimethyl Sulphate	

Table 4. Herbicides restricted for use in the country

S.No.	Name of herbicides	Details of Restrictions
1.	Dazomet	The use of Dazomet is not permitted on Tea. (S.O.3006(E) dated 31st Dec, 2008)
2.	Trifluralin	(i) The Registration, import, manufacture, formulation, transport, sell and its all uses except use in wheat shall be prohibited and completely banned from 8th August, 2018. (ii) A cautionary statement has to be incorporated in the label and leaflet that it is toxic to aquatic organism, hence should not be used near water bodies, aquaculture or pisciculture area (vide S.O 3951(E) dated 8th August, 2018).

3. Non compliance of label claims

Never the less many herbicides which are under proposed list of restriction /banned do not comply with recommended or approved use by the Central Insecticidal Board. For example, atrazine is approved for maize and sugarcane and paraquat dichloride is approved for 10 crops (Tea, potato, cotton, rubber, rice, coffee, wheat, maize, grapes, apple) (Directorate of Plant Protection, Quarantine and Storage, 2023) but field uses were reported in 19 crop for atrazine and 23 crops for paraquat, respectively (Downtoearth, 2022) which showed unethical and non-judicial use of herbicides in India. Committees come up with a decision on glyphosate and this can be used in non-crop area only by the Pest Control Operator. However, the government has not banned the sale, distribution and use of glyphosate or any other herbicides. That contain glyphosate. It is astronishing that the proposed banned list of 8 herbicides that comprised of 60.3% consumption of the total registered herbicides in India in 2022.

Repeated or unauthorized uses and herbicide exposure makes farmers at high risk as they are less or poorly literate and do not recognize the extent of risks or health hazards. While putting retraction/ban on these herbicides by the registration committee based on environmental and human concern, it was suggested that several alternate herbicides are available in place of proposed list of restriction /banned and, hence, the ban will not affect weed management.

The review of pesticides is done by constituting expert committees. Based on the recommendations of such international expert committees, agencies and based on toxicity data toxicity, the World Health Organization classifies certain pesticides as extremely hazardous (Class Ia) and highly hazardous (Class Ib). Toxicity and registered formulations of herbicides which are under proposed restriction /ban are presented in **Table 5 and 6**. In view of adverse effects of synthetic herbicides, the government is promoting use of biopesticides, which are generally considered as safer than chemical herbicides. The approved list of all herbicides on various crops are displayed in public domain on the official website of the Directorate of Plant Protection Quarantine & Storage (**Table 5**).

Table 5. List of prohibited herbicides by The Gazette of India CG-DL-E-18052020-219423, Extraordinary, PART II Section 3 Sub-Section (Ii), New Delhi, Monday, May 18, 2020/Vaisakha 28, 1942, No. 1351], Published on 14 May 2020 and their registered formulation as on 13 July 2023. **https://www.efsa.europa.eu/en/news/glyphosate-no-critical-areas-concern-data-gaps-identified**

No	Name of herbicide	Decision of the Central Government	Registered formulation
1.	Atrazine	1. Incomplete bio-efficacy data submitted i.e. Study on leaching. 2. There are reports pertaining to its Endocrine Disruption potential in public domain.	50% WP

Table contd....

		3. It is banned in 37 countries, not approved in EU vide Legisl.2004/248/EC, EU, UK, Chad, Details of country (As per PAN data) Gambia, Mauritania, Niger, Oman, State of Palestine, Senegal, Tongo, Cabo Verde. 4. Alternatives are available for use. 5. The product is toxic to aquatic organism including fish. Therefore, import, manufacture, sale, transport, distribution and its use shall be prohibited in agriculture.	
2.	Butachlor	1. Incomplete bio-efficacy studies submitted. In addition, they have not generated fresh bio-efficacy and residue data. 2. Prone for leaching. 3. It is banned in 31 countries, not approved in EU vide Legisl. 2002/2076/EC Details of country (As per PAN data) EU,UK 4. Alternative are available for use. 5. The product is toxic to aquatic organism including fish. Therefore, import, manufacture, sale, transport, distribution and its use shall be prohibited in agriculture from publication of this order.	50% EC; 50% EW
3.	2,4-D	1. Concentration of dioxin content, as it is carcinogenic, is required to be monitored. 2. In addition, incomplete data submitted for sugarcane, potato and maize. 3. The product falls under category 2 of European Union prioritization of Endocrine Disrupting Chemicals and also figure in Tier 1 screening final list of Endocrine Disruption Screening Program (EDSP) 4. It is banned in 3 countries, Inactive (EPA) 5. Alternatives are available for use. 6. Therefore, import, manufacture, sale, transport, distribution and its use shall beprohibited in agriculture.	Amine Salt 58% SL Ethyl Ester 20% WP Ethyl Ester 38% EC Ethyl Ester 4.5% GR Sodium Salt WP 80%
4.	Diuron	1. The product falls under category 2 of European Union prioritization of Endocrine Disrupting Chemicals and also figure in Tier 1 screening second list of Endocrine Disruption Screening Program (EDSP). 2. Data on bio-efficacy, persistence and residue has not been submitted for fixation of waiting period on Rubber, Citrus (sweet orange), Banana & cotton crops.	80% WP

Table contd....

		3. However, incomplete data submitted for grapes. 4. Banned in Mozambique.	
5.	Oxyflourfen	1. Alteration in blood parameters causes' anemia, hemolytic consequences, Liver and in liver. Possible human carcinogen. The product falls under Tier 1 screening second list of Endocrine Disruption Screening Program (EDSP). 2. Data on residue and persistence for Rice (Direct sown as pre-emergence), groundnut, Onion & Potato crops not submitted. 3. Potential to affect terrestrial plants and aquatic ecological systems. Sub chronic effects and chronic seen in birds. 4. It is banned in 02 country, Inactive (EPA); Mozambique 5. Alternatives are available for use. 6. It is toxic to aquatic organisms including fish and is possible human carcinogen. Therefore, import, manufacture, sale, transport, distribution and its use shall be prohibited in agriculture from publication of this order.	0.35% GR 23.5% EC 20% DF
6.	Pendimethalin	1. Incomplete toxicity data submitted. Also, stakeholders have not submitted the clarification on the studies submitted with respect to aquatic organisms. Not submitted data on residue and persistence on rice crop. 2. Causes thyroid follicular cell adenoma. 3. It is banned in 02 countries, Inactive (EPA); Norway. 4. Alternatives are available for use. 5. It is highly toxic to aquatic organisms including fish. Therefore, import, manufacture, sale, transport, distribution and its use shall be prohibited in agriculture.	0.35% GR 23.5% EC 20% DF
7.	Sulfosulfuron	1. Stakeholders submitted multi-locational studies to check the possible development of resistance in the target weeds in Punjab, Haryana and Uttarakhand. 2. Further, as per report 32.5% resistance was observed against target weed *Phalaris minor* in Punjab and Haryana while no resistance is observed in Uttarakhand.	75% WG

Table contd....

		3. It is banned in 01 country. Details of country (As per PAN data) Norway. 4. Several alternatives are available for use. 5. The product is resistant against the target weed. 6. Therefore, import, manufacture, sale, transport, distribution and its use shall be prohibited in agriculture.	
8.	Glyphosate	Banned in 28 countries/ 36 Argentina; Australia (in some states); Belgium; Bermuda; Bahrain; Barbados; Brazil; Canada (8 out of 10 provinces); Colombia; Costa Rica; Czech Republic; Denmark; El Salvador; Fiji; France; Germany; India; Italy; Luxembourg; Malta; Netherlands; Oman; Qatar; St. Vincent and the Grenadines; Saudi Arabia; Portugal; Scotland; Slovenia; Spain; Sri Lanka; Thailand; Vietnam; Austria. (https://biodx.co/28-countries-ban-the-use-of-glyphosate-key-ingredient-in-roundup/)	20.2% SL (IPA Salt) 41% SL (IPA Salt) 54% SL (IPA Salt) Ammonium Salt 20% SL Ammonium Salt 5% SL Ammonium Salt 71% SG Potassium Salt 41.60% w/w SL (Equivalent to 54% w/v)

Table 6. Oral LD_{50} value and toxicity rating of listed herbicides under restriction/ban

Herbicide name	Oral LD_{50} (rat)(mg/kg)	Toxicity rating*
2,4-Dichlorophenoxy acetic acid	375-1200	II-III
Atrazine	3090	III
Butachlor	3300	III
Diuron	3400	III
Glyphosate	>2000	III
Oxyfluorfen	>2000	III
Pendimethalin	4050	IV
Sulfosulfuron	>5000	IV

*I: Extremely hazardous, II: Highly hazardous, III: Moderately hazardous, IV: unlikely to pose any hazards

4. Pesticide consumption pattern in India

In India, currently pesticides is being used in around 52.1% cultivated area among total pesticide use in the country, herbicide is used in approximately 16% area **(Table 7)**. Total pesticide consumption is the highest in Utter Pradesh followed by Maharashtra, Punjab, Telangana, and Haryana, which is followed by West Bengal, Andhra Pradesh, Karnataka and Chhattisgarh. On the other hand, per hectare consumption of pesticides was the highest in Telangana (1.01 kg) followed by Punjab (0.652 kg), Haryana (0.625 kg), Utter Pradesh (0.451 kg), West Bengal (0.361 kg) and TamilNadu (0.321 kg) during 2022-23 **(Table 7)**.

Table 7. All India statistics of area under cultivation and under use of chemical as on July 13, 2023 source statewise_consumption_of_chemical_pesticides.xls (live.com)

Year	Area under Cultivation ('000' Hectare)	Use of pesticides (MT)	Area under pesticide use (%)	Herbicide use (MT)	Herbicide use (%)
2018-19	141555	81120	57.3	3998	15.4
2019-20	198552	108035	54.4	4275	15.81
2020-21	188595	111289	59.0	3297	13.6
2021-22	195875	96042	49.0	2920	12.48
2022-23	207562	108216	52.1	4155	16.54

Consumption of herbicide under proposed list of ban/restriction is given in Table 8. The proposed banned list of 8 herbicides that comprised of 60.3% consumption of the total registered herbicides in India in 2022 **(Table 8, Figure 1 and 2)**.

Table 8. Consumption of herbicide under proposed list of ban/restriction in India during 2018 -23 as per 13 July 2023 (Consumption MT, Tech Grade)

No.	Herbicide under list	2018-19	2019-20	2020-21	2021-22	2022-23
1.	2,4-D (Amine Salt, Chlorophenoxy Acetic Acid; Ethyl Ester and Sodium Salt	916.53	1140.36	947.86	1043.94	1018.01
2.	Atrazine	387	346.26	287.82	293.78	329.24
3.	Butachlor	565.24	354.1	209.17	212.58	335.75
4.	Diuron	56.53	12.46	11.54	5.98	19.85
5.	Glyphosate	679.81	571.49	505.19	561.71	579.92
6.	Oxyfluorfen	16.37	17.66	34.16	27.56	27.74
7.	Pendimethalin	137.69	198.94	149	201.92	193.75
8.	Sulfosulfuron	NA	NA	NA	NA	NA
	Total	**2758.87**	**2641.3**	**1995.74**	**2347.47**	**2504.26**
	Share of 8 herbicides (%)	69.01	61.78	60.53	80.4	60.3

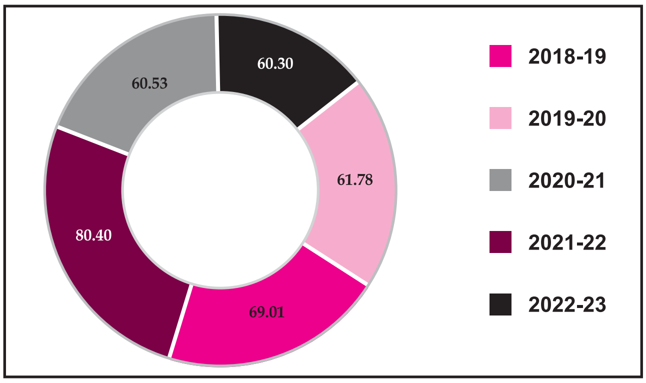

Figure 1. Percent use of listed herbicides out of total consumption of herbicides in India during 2018-2023

Weed management is a difficult task in various crops due to presence of diversity of weeds with difference tolerance levels for herbicides therefore selective herbicide are being recommended in various crops based on weed flora and tolerance to the crop plants.

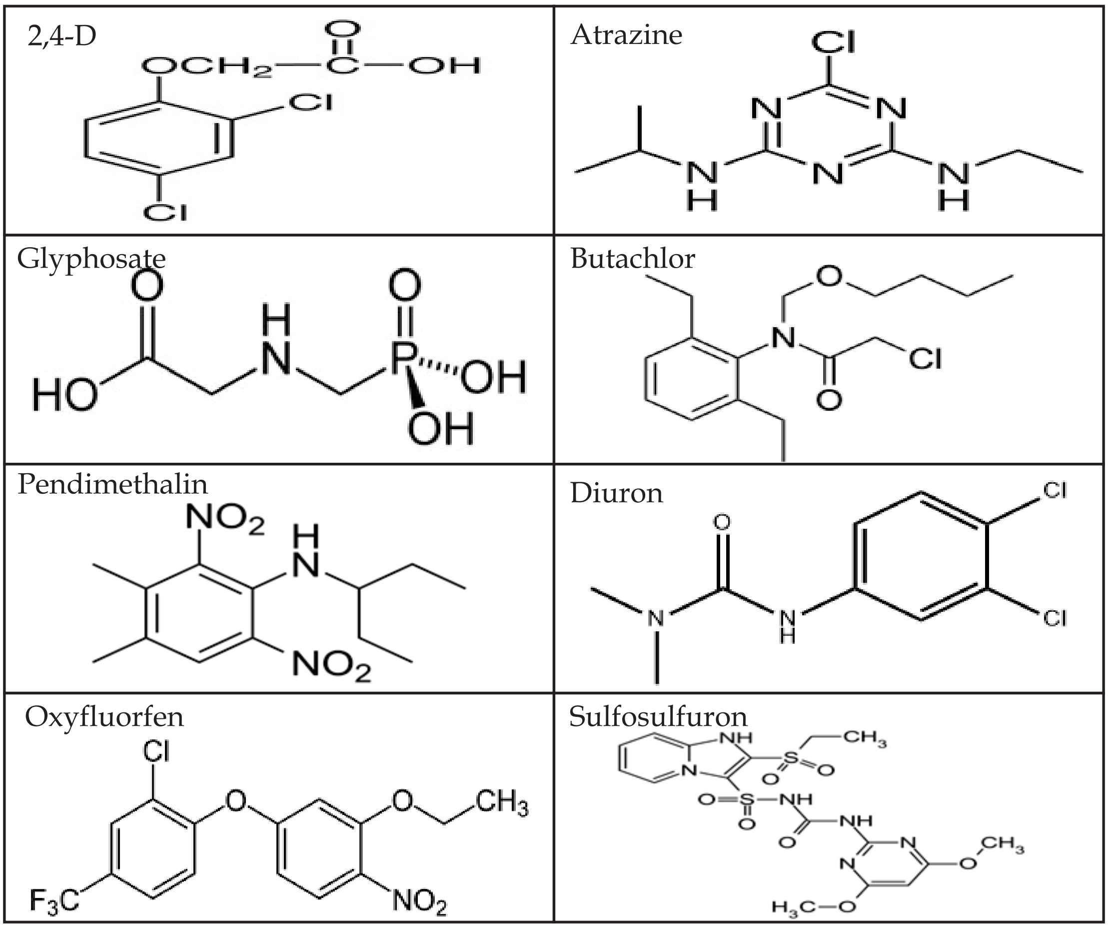

Figure 2. Chemical structure of herbicide under proposed list of ban/restriction

Presently 65 herbicides are registered in India for weed management in various crops (**Table 9).** Among these registered herbicides, 8 are under proposed list of restriction/ban.

Table 9. Herbicide registered in India as of 13 July 2023 (Source PPQ)

Name of Herbicide			
1.	2,4-D	34.	Propanil
2.	Ametryn	35.	Diclosulam
3.	Anilofos	36.	Diuron
4.	Atrazine	37.	Ethoxysulfuron
5.	Azimsulfuron	38.	Fenoxaprop-p-ethyl
6.	Bensulfuron Methyl	39.	Florpyrauxifen-benzyl
7.	Bentazone	40.	Fluazifop-p-butyl
8.	Bispyribac Sodium	41.	Flucetosulfuron
9.	Butachlor	42.	Fluchloralin
10.	Carfentrazone ethyl	43.	Flufenacet
11.	Chlorimuron Ethyl	44.	Flumioxazin
12.	Cinmethylin	45.	Flurochloridone
13.	Clethodim	46.	Fluroxypyr meptyl
14.	Clodinafop- propargyl	47.	Fluthiacet methyl
15.	Clomazone	48.	Glufosinate Ammonium
16.	Cyhalofop-butyl	49.	Glyphosate
17.	Diclofop-methyl	50.	Halosulfuron methyl
18.	Isoproturon	51.	Imazethapyr
19.	Metamifop	52.	Propaquizafop
20.	Metamitron	53.	Pyrazosulfuron-ethyl
21.	Methabenzthiazuron	54.	Pyrithiobac Sodium
22.	Metolachlor	55.	Pyroxasulfone
23.	Metribuzin	56.	Quinclorac
24.	Metsulfuron-methyl	57.	Quizalofop-ethyl
25.	Orthosulfamuron	58.	Quizalofop-p-tefuryl
26.	Oxadiargyl	59.	Saflufenacil
27.	Oxadiazon	60.	Sulfentrazone
28.	Oxyflourfen	61.	Sulfosulfuron
29.	Paraquat dichloride	62.	Tembotrione
30.	Pendimethalin	63.	Topramezone
31.	Penoxsulam	64.	Triallate
32.	Pinoxaden	65.	Triasulfuron
33.	Pretilachlor		

5. Herbicide degradation and persistence

Herbicides persistence in the soil may be predicted based on the half-life or time required to degrade fifty percent of the original molecule in the soil (**Table 10**). Half-life depends on the soil texture and weather conditions, and rate of application of the herbicide applied. Heavy rainfall will cause greater leaching and runoff. Sandy soil would have a higher leaching potential than a clay soil due to larger pore spaces and lower CEC (Sondhia and Yaduraju 2005, Sondhia 2007, 2009). Higher humidity generally enhances the soil microflora proliferation. The persistence of herbicides are generally govern by biochemical degradation in the soil.

Jhala et al. (2010) reported 44.93 to 39.09 days half-life of pendimethalin at the rate of 0.5 and 1.0 kg /ha in sandy loam soil with and without addition of farmyard manure (FYM) under Middle Western Indian agro-climatic conditions in Indian mustard (*Brassica juncea* L.). Half-life of 11.23-19.83 days for pendimethalin in the field peas (*Pisum sativum* L.) and chickpea soil was reported (Sondhia 2012, 2013). Kulshrestha et al. (2000) reported rapid degradation of pendimethalin in each year with each successive crop. Pahwa and Bajaj (1997) reported direct correlation in pendimethalin persistence in soil with temperature and application rate. Pendimethalin persisted up to 200 days and caused phytotoxicity to the succeeding sensitive sorghum crop in a sandy loam soil applied at 1.0 to 4.0 kg/ha rates in wheat crop. Pendimethalin was found to be persistent in soil of cabbage field however residues did not found in plant parts (Arora and Gopal 2004).

Faster dissipation of oxyfluorfen is reported in wheat plants than in soil, with a mean half-life of 6.1 and 11.2 days. A sorption study revealed that the adsorption of oxyfluorfen to the soil was highly influenced by the soil organic carbon with the K_{oc} value of 5450.

Sondhia et al. (2006) reported rapid dissipation of butachlor in rice field as compared to laboratory conditions with half-life of 18.11-23.0 days at 1.0 -2.0 kg/ha. 2, 4-D at 0.4 kg/ha alone and in combination with anilofos persisted up to harvest with half-life of 18-22 days (Jayakumar and Sree Ramulu 1993). In a monitoring study, butachlor residues contributed 61% and pendimethalin (36%). The pendimethalin and butachlor residues ranged from 0.03-1.28 ng/g and 0.02-1.22 ng/g, respectively (Bhupander 2011).

Diuron residues at 3 kg/ha application rate persisted on top 2.5 cm of the soil profile even after eight months (Leela 1984).

Sondhia (2001, 2002), and Janaki et al. (2012) reported more than 95% atrazine dissipation from the field at the time of crop harvest with the reported half-life of 9.38-21.54 days in soil. Pre-emergence applications of atrazine at 1.5 kg/ha application rate persisted up to 47 (Neelam et al. 1997). Atrazine residues in the soil of maize crop were not found at harvest whereas 0.056 mg/kg of residue in the post-harvest soil were found (Janaki et al. 2012). Atrazine and its metabolites, de-isopropyl atrazine (DIA) and deethylatrazine (DEA) had a significant amount of leaching potential and can contaminate surface and groundwater and posed unacceptable risks to springtail *Folsomia candida*, earthworm *Eisenia fetida* and cause toxicity to a variety of freshwater fish, aquatic arthropods, amphibians, and aquatic invertebrates (Bhatti et al. 2022).

Table 10. Half-lives of herbicides in soil in India (Source: Sondhia and Varsheny 2010) which are under proposed list of restriction/ban

Herbicides name	Half-lives (Days)
2, 4 D	7-22
Atrazine	13-58
Butachlor	5-24
Diuron	-
Glyphosate	6-19
Oxyfluorfen	12-29
Pendimethalin	15-77
Sulfosulfuron	3-27

Glyphosate persisted in the soil up to 30 to 60 days at application doses of 0.5 to 2.0 kg/ha. Glyphosate residues in the tea leaves were detected up to 15 days and residues were reported to be below the maximum residue limit at harvest (10 mg/kg). Half-lives of glyphosate ranged from 5.80 to 19.10 days in the soil and 5.82 to 7.91 days in the tea leaves at the three doses. (Bandana et al. 2015). Persistence of some herbicides under Indian tropical conditions in soil is given in **Table 11**.

Table 11. Persistence of proposed restriction/ban of herbicides under Indian tropical conditions in soil in India

Herbicide	Persistence in soil (days)	Reference
Atrazine	45-90	Neelam et al. 1997, Sondhia 2014
2, 4-D	45-90	Sushilkumar et al. 2003, Kumari et al. 2004, Sondhia 2014
Butachlor	100	Sondhia et al. 2006
Diuron	>240	Leela 1984
Glyphosate	60	Bandana et al. 2015
Oxyflourfen	60-80	Devi et al. 1998
Sulfosulfuron	90-150	Ramesh and Maheshwari 2003, Sondhia and Singh 2008
Pendimethalin	60-200	Rai et al. 2000, Sondhia 2012, 2013, 2014

Sulfosulfuron residues in soil at 25 -50 g/ha application rates were not detected at harvest in wheat crop (Ramesh and Maheshwari 2003, Sondhia and Singh 2008). However after150 days, residues were found below 0.001 µg/g in soil samples collected from 25 to 50 g /ha treated plots (Sondhia and Singhai 2008).

6. Herbicide residues in food grain

The analytical results of herbicide residues in various crops indicated global presence of residues but below the maximum residue levels in most of the cases. Using the latest hi-tech analytical devices the presence of herbicide residues can be easily detected at ppb or even low level. Based on extensive herbicide residue work conducted at ICAR-Directorate of Weed Research, Jabalpur, All India Coordinated project on Weed management (AICRP-WM) and various sources in India, in approximate 80 % samples residues were found below the detection limit (BDL), 13.4% below maximum residue limit (MRL) and approximately 6.6 % residues were found above MRL values.

In paddy straw 0.01-0.03 µg/g oxyfluorfen residues were reported at 240- 500 g/ha rates. Residues were 0.028-0.03 µg/g in soil when oxyfluorfen was applied at 240-500 g/ha rates. However, in rice grains, 0.018-0.106 µg/g of oxyfluorfen residues were detected in 240-500 g/ha treated plots (Sondhia 2009). In plant foliage collected at harvest, traces of atrazine residues were detected in few samples in first year but in the second year's residues were not detected (Nag and Das 2009).

Butachlor dissipated with half-life varying from 12.5 to 21.5 days at 1.0 and 2.0 kg/ha application rates under with and without organic manures conditions. Low levels of residues were detected in rice grain (Rao *et al.* 2012). However Devi et al. (1997) reported that butachlor residues in rice crop were found below the maximum permissible residue limit (0.25 mg/kg) in soil. Harvest time samples of paddy grains, rice bran and straw treated with butachlor showed residues below the detectable levels in rice, 0.002 mg/kg in bran, 0.009 mg/kg in straw and 0.006 mg/kg in rice grains at 1.0 and at 2 kg /ha, the residue were 0.001, 0.005, 0.010 and 0.025 mg/kg in rice, bran, straw and paddy grains, respectively (Reddy et al. 1998). Sondhia et al. (2004) reported that butachlor residues were not detected after 120 days in clay loam soil applied at 1.0 kg/ha in transplanted rice crop.

Sulfosulfuron residues were not reported in wheat grains, straw and subsequent vegetables in natural ecosystem as well as in model ecosystem at recommended rates in wheat crop (Ramesh and Maheshwari 2003, Sondhia et al. 2007, Sondhia and Singhai 2009). Herbicide residues in crop plants at harvest are given in **Table 12**.

Table 12. Residues of listed herbicides in the soil, food grain and straw

Herbicides	Crop	Dose (kg/ha)	Residues (µg/g)			References
			Soil	Grains	Straw /other plant, product	
2,4-D	Wheat	0.5-2.0	<0.02	<0.02	<0.02	Sharma et al. 2013
Atrazine	Maize	0.5 &1.0	BDL	0.056	BDL	Janaki et al. 2012
Butachlor	Rice	1.0	0.005	0.025-0.002	0.029-0.006	Reddy et al. 1998, Deka and Gogoi 1993, Sondhia et al. 2006
Diuron	Sugarcane	2-4	BDL	-	BDL	Tendon and Pant 2019
Glyphosate	Tea	1-2	0.002-0.012	-	BDL	Sharma et al. 2015
Oxyfluorfen	Rice	0.150-0.250	BDL	0.018	0.106	Sondhia 2009
Pendimethalin	Onion Chickpea	0.750-0.185	BDL	0.004-BDL	0.007-0.001	Sondhia 2013a, 2013b
Sulfosulfuron	Wheat	0.025	BDL	0.010- BDL	0.004- BDL	Ramesh and Maheshwari 2007, Sondhia et al. 2007

*Source: (Sondhia 2007, 2010, 2014, 2018) **BDL-Below detection limit

Information on the use of these herbicide against various weed in crop and also one hand information on availability of other alternative herbicide that can be used to control weed in suggested crops is given in **Table 13**.

Table 13. Use of Herbicide under consideration in various crops and alternative herbicides

Herbicide	Mode of application	Application in crops		Bioefficacy against weeds and crop	Effectiveness of other herbicide in place of herbicide mentioned*	Phytotoxicity to crop/weeds	Reference
		Approved Label claim by CIB&RC	Other uses withoutlabel claims by CIB&RC				
2,4D EE 2,4D Sodium salt	Pre and post	Maize, wheat. rice, sorghum, sugarcane Citrous, Grapes Maize, Sugarcane Wheat, Aquatic weeds	Pearlmillet barley -	Effective against broad leaved weeds	For maize in place of 2,4-D topramezone is being used Wheat – Carfentrazone control *Solanum, C. arvensis, Malwa* which are not controlled by 2, 4-D. *Rumex* and *Medicago* are controlled by Metsulfuron. Rice- Almix and ethoxysulfuron	Due to drift of 2, 4 D toxicity occur in cotton and mustard at Hisar.	Chaudhari 2017
Atrazine	Pre – mergence	Maize, sugarcane,	Pearlmillet, Bajra, sorghum	Effective weed control against broad leaved weeds	*Kharif* maize Tembotrione, Topramezone Atrazine + Halosulfuron methyl Topramezone + Topramezone Metribuzin (sugarcane) Tembotrione (maize)	Not observed at recommended dose	Patel, et al. 2006; 2018; 2019
Butachlor	Pre-emergence	Rice,	Vegetable, Groundnut, Maize, Sorghum Oil Seeds Okra Tomato	Mainly grassy weeds	Okra Oxadiargyl, Quizalofop –ethyl Cyhalofop- butyl, Fenoxaprop -p-ethyl Tomato: Alachlor, Fluchloralin, Trifluralin, Oxadiazon, Metribuzin Onion: Fluchloralin, Isoproturon Rice: Pretilachlor, Anilofos, Oxadiargyl	Not observed at recommended dose	Patel et al. 2004a, b
Diuron	Post-emergence		Potato and protected spray in wider field crops and plantation crop	Grassy and broad leaved weeds	Potato: Fluchloralin, Paraquat	Not observed at recommended dose	AICRP-WM reports
Glyphosate	Post-emergence	Non-crop area Tea		Major weeds	Cotton Quizalofop-ethyl, Fenoxaprop-p-ethyl Pyrithiobac-sodium + quizalofop-p-ethyl, Paraquat	Not observed at recommended dose	AICRP-WM reports
Oxyfluorfen	Early post emergence	Rice, Tea, Groundnut onion, menthe	garlic, chickpea, chili, tobacco, cumin blackgrass		Summer groundnut : Quizalofop-ethyl, Imazethapyr, Imazethapyr + imazamox Fluazifop-p-butyl + fomesafen Onion: Oxadiargyl Chickpea: Oxadiargyl. Imazethapyr Blackgram:Quizalofop-ethyl,	Not observed at recommended dose	Patel, et al. 2017, 2018, 2020a, b , Chaudhari et al. 2020.

Table contd...

					Imazethapyr, Fenoxaprop-p-ethyl Green Chili: Fluchloralin, Metolachlor, Oxadiazon Tobacco: Benthiocarb, Fluchloralin Cumin, Fluchloralin, Trifluralin, Isoproturon		
Pendimethalin	Pre-emergence	wheat, rice, Cotton, pegeonpea, Soybean pulses, chili onion, mustard cumin	*Cuscuta* in forage lucerne Garlic	Complex weed flora except *Cyperus* and *Digera*	Greengram: Imazethapyr, Imazethapyr+imazamox, Quizalofop-ethyl,Fenoxaprop-p-ethyl Soybean: Carfentrazone, Clomazone, Diclosulam, Quizalofop-ethyl , Imazethapyr, Imazethapyr + imazamox Propaquizafop + imazethapyr, Sodium acefluorfen + clodinafop propargyl, Fluazifop-p-butyl +fomesafen Wheat: Clodinafop, Clodinafop+ metsulfuron, Metsulfuron methyl, Mesosulfuron+ iodosulfuron Cotton: Quizalofop-ethyl, Fenoxaprop-p-ethyl, Pyrithiobac-sodium+ quizalofop-p-ethyl, Paraquat *Kharif* maize: Topramezone, Tembotrione Onion: Oxadiargyl Chickpea: Oxadiargyl, Imazethapyr, Fluchloralin Cluster Bean: Imazethapyr, Propaquizafop Blackgram: Quizalofop-ethyl, Imazethapyr, Fenoxaprop-p-ethyl Okra: Oxadiargyl, Quizalofop–ethyl Cyhalofop- butyl, Fenoxaprop-p-ethyl Cumin: Fluchloralin, Trifluralin, Isoproturon Green Chili Fluchloralin, Metolachlor, Oxadiazon Tomato: Alachlor, Fluchloralin, Trifluralin, Oxadiazon, Metribuzin Chicory Fluchloralin, Trifluralin Isabgul: Isoproturon	Not observed at recommended dose	Barevadia et al. 1997 Chaudhari, et al. 2017, 2019, 2020. Patel, et al. 2008, 2016, 2018 2019a, b, 2020. Mishra, et al. 2017. Patel et al. 2004.
Sulfosulfuron	Post-emergence	Wheat	Orobanche control in tomato	Broad leaved weeds	Wheat: Clodinafop, Clodinafop + metsulfuron, Metsulfuron methyl Mesosulfuron + iodosulfuron Clodinafop, meso + iodosulfuron(RM), pinoxaden against grassy weeds	Not observed at recommended dose	Chaudhari et al. 2017

*Based on Information collected from AICRP-WM centre, without label claim

7. Herbicide residues in vegetables, pulses, oilseed, tea and other crop

Sondhia (2013) reported terminal residues of pendimethalin in the green field peas (*Pisum sativum* L.) and chickpea (*Cicer arietinum* L.) at 750-185 g/ha application rates. Low pendimethalin residues were found in mature pea grain (0.004-BDL µg/g), and straw (0.007-0.001 µg/g) at 750- 185 g/ha treatments, respectively. Pendimethalin residues were 0.025, 0.015 and <0.001 µg/g in chickpea grains at 750 to 185 g/ha treatments. Much lower pendimethalin residues *viz*. 0.015 to <0.001 µg/g were found in straw at 750, 350 and 185 g/ha treatments, respectively (Sondhia 2012). Terminal residues of pendimethalin (applied as pre-emergence at 1.0 kg/ha) in tomato, cauliflower, and radishes were reported to be 0.008, 0.001 and 0.014 µg/g, respectively (Sondhia 2013). Residues of pendimethalin, were found below the maximum residue limit in onion bulbs at harvest (125 days after spraying) at Anand. Sondhia and Dubey (2006) did not found pendimethalin residues at mature stage, however, 0.007 µg/g pendimethalin residues were detected in green onion at 1.0 kg/ha application rate. The half-life of pendimethalin in onion plants and soil varied from 11.8- 15.5 days and 14.9-15.1 days, respectively (Sinha et al. 1996).

At Anand, pendimethalin application at 0.6-0.9 % to tobacco crop resulted in 0.198 to 0.720 mg/kg residues in tobacco leaves and 0.04-0.079 mg/kg residues treated with 0.25% pendimethalin (Parmar et al. 1998). Pendimethalin residues at 0.5 kg/ha application rate were not detected in the soil of lucerne crop at Anand. At harvest the level of pendimethalin residue (applied as pre-emergence 1.0 - 0.5 kg/ha) in onion bulbs ranged from 0.003 to 0.021, 0.004 to 0.036 and 0.080 to 0.104 µg/g, respectively. Marginal increase in the residue was observed with increased FYM application (Raj et al. 1999). Sirestha et al. (2011) reported persistence of pendimethalin and oxyfluorfen in soil and its residues in edible parts of radish. At harvest more than 98% of initial deposit of pendimethalin was dissipated and observed half-life in radish field was 6.45 days and 10.03 days at 0.5 and 0.75 kg/ha applied rates, respectively. Samples of onion bulbs collected at 30, 60 and 90 days after spray and at uprooting stage showed no residues of oxyfluorfen and pendimethalin in onion bulbs (Kaur et al. 2010).

Sondhia and Dixit (2007) and Sondhia (2014) reported terminal residues of oxyfluorfen in the green onion and mature onion bulbs as 0.041- 0.063 and 0.0034-0.0460 µg/g at 150–300 /ha rates. Residues of oxyfluorfen applied in mature onion were below the maximum residue limit (0.05 µg/g). A pre-harvest interval of 118 days for onion crop after the herbicide application was suggested (Sondhia 2010). Oxyfluorfen residues (applied to cabbages at 0.1 to 0.4 kg/ha application rates) were not found in soil at harvest (Sundararajan et al. 1993). More than 60% of the initial deposit of oxyfluorfen was dissipated at the time of harvest of crop and 6.96 and 12.26 days of half-life of oxyfluorfen was observed at 0.1 and 0.15 kg/ha, respectively after application. Pendimethalin and oxyfluorfen residue were below maximum residue limits in radish tubers (Sirestha et al. 2011).

Malformation in leaves by 2, 4-D residues at 0.06 mg/kg level is reported by Kathpal et al. 1980.

Atrazine was reported to be degraded to undetectable levels at all applied doses by the time the maize crop was harvested (90 days) with the half-life of 23 to 31 days in the soil. However, maize yield decrease to 32.0 and 25.2 q/ha when compared in the hand-weeded treatment at 2.0 kg/ha application rate. However, atrazine had no significant residual effect on chickpea or Indian mustard yields (Saikia et al. 2000). Sondhia (2000) reported 0.088 mg/kg atrazine residues in maize grains at 2.0 kg/ha application rate.

8. Herbicide residues in water system

Herbicide enters into streams and underground water sources by runoff, drift and leaching mechanism. Many herbicides are routinely detected from the surface and ground water sources in developed countries mainly in central and western United States (Mississippi and Sacramento), Argentina (Parana), India (Ganges), East China (Yangtze, Pearl and Yellow River) and South East Asia (Irrawaddy and lower Mekong). The most often detected herbicides above the prescribed maximum residues limits are 2, 4-D, atrazine, diuron, glyphosate, butachlor, pendimethalin, oxyfluorfen, etc. Many herbicides are strictly banned or restricted such as butachlor, atrazine, pendimethalin in USA and European countries due to their high concentration in the ground and surface water and potential health hazards to aquatic, animal and human lives. It was identified that 82% of herbicides degraded into other molecules while 10% remained as residues in the soil. Another 7.2%, about 68,000 tons, leached into aquifers – rocks or sediment that hold groundwater.

Persistence and mobility of 2, 4-D was found to be dependent on soil water content (Gupta et al. 2012). Reddy and Reddy (2010) reported atrazine residues (NO-1.056 µg/L) in Singoor reservoir, Hyderabad and 0.056 µg/L in Osmansagar water, however 0.01 to 0.093 mg/L butachlor residues were reported in the water of rice field at Bangalore (AICRP weed control Bengaluru). 2,4-D increased pH, EC, carbonates and free CO_2 increased after treatment at 1.0-2.0 mg/kg dose but the dissolved oxygen decreased and the 2, 4 -D residues become non-detectable after 42 days. 2, 4-D residues at below the acceptable daily intake (0.01 mg per kg body weight) were detected in fish samples at Thrissur at recommended rate and at higher dose *viz* 2.0 or 4.0 kg/ha and a waiting period of more than 4 month is suggested.

Pendimethalin could leach in the clay loam soil up to the depth of 55 cm in 200 mm rainfall condition (Sondhia 2007).

The total mean concentration of atrazine ranged from 0.72 to 17.3 µg/L in groundwater samples collected from Delhi (Aslam et al. 2013).

Yadav et al.(2013) reported genotoxic potential of butachlor even at low dose level (1.0 mg/kg) and suggested that butachlor interferes with cellular activities in fishes at genetic level inducing chromosomal aberrations and suggested a serious concern towards the potential danger of butachlor for aquatic organism. Tilak (2007) reported 0.1255 mg/kg butachlor residue in gills, 0.3515 mg/kg in (Bloch) liver, 0.3145 mg/kg in kidney and 0.2350 mg/kg butachlor residues in brain traces muscle of *Channa punctate* after an exposure of 10 days to sub lethal concentration (1/5th of static LC50) of butachlor. Muniappa et al. (1995) reported high fish mortality with 2, 4-DEE and paraquat than with glyphosate.

In long term bio-accumulation of sulfosulfuron in the fish conducted in glass aquarium for 90 days at 25- 100 g/ha resulted in 1.09- 3.52 µg/g sulfosulfuron residues after 10 days and by 90 days residues in the fish body were below the MRL (Sondhia 2008). In another indirect effect of herbicides, fish mortality was more with butachlor followed by anilofos and oxyflourfen (Sondhia 2012). Sondhia (2009) reported initial concentration of sulfosulfuron residues in the surface soil (0-15 cm) were 0.229, 0.967 and 1.038 µg/g which dissipated to 0.003- 0.005 µg/g at 25- 100 g/ha doses by100 days. However, at initial days sulfosulfuron residues in sub-surface soil were 0.136-0.065 µg/g in 25-100 g/ha doses. Sulfosulfuron residues were not detected after 200 days in surface and sub-surface soils in all the doses. Ramesh et al. (2007) reported DT_{50} and DT_{90} values 67-76 and 222-253 days of sulfosulfuron in natural water at 1 and 2mg/L levels. Bioaccumulation of sulfosulfuron in fish was conducted under static conditions exposing the fish at one-tenth of sub-lethal concentration 9.0 mg/L and at double the concentration 18mL/g for a period of 56 days. Accumulation of sulfosulfuron in fish in the range 0.009-0.496 µg/g was reported. Both in water and fish samples, metabolites of aminopyrimidine, desmethyl sulfosulfuron, guanidine, sulfonamide, ethyl sulfone and rearranged amine were detected. One of the metabolite aminopyrimidine was identified at higher concentration levels (0.01-0.1µg/mL) in comparison to other metabolites (Ramesh et al. 2007 and Sondhia 2008). The DT_{50} and DT_{90} values for aminopyrimidine dissipation in water were found to be 66-68 days and 218-226 days and in subsoil,105 to 147 days and DT_{90} values 349 to 488 days.

9. Effect of herbicide on human heath

However no direct adverse effect on human after herbicide application for weed management is reported, still several reports indicate that herbicide poisonings have been rising sharply for years in India and across the world. Based on recent study conducted by University of Sydney scientists and the Food and Agriculture Organization of the UN, pesticides from farming leach into world's waterways at rate of 710 tons a year, and safe levels exceeded in 13,000km of rivers globally with ingredients potentially degrading into more persistent substances (Maggi et al 2023). Deaths related to intentional herbicides poisoning in India are reported. Increasing incidences of acute herbicide self-poisoning by butachlor, paraquat, 2, 4-D, pendimethalin, glyphosate etc. are an emerging significant problem in parts of Asia including India (Singh 2012, Sondhia 2014).

The oxidative role of butachlor in intracellular ROS production, and consequent mitochondrial dysfunction, oxidative DNA damage and chromosomal breakage, which eventually triggers necrosis in human PBMN cells is also reported (Dwivedi et al. 2012). In an Indian series of 17 patients of herbicide poisoning, the most common symptoms were vomiting (100%) followed by altered sensorium (59%), oral ulceration or dysphagia (53%), dyspnea (41%) or loose stools (24%) (Sandhu et al 2003).

Though 2,4-D has a moderate mammalian toxicity and human poisoning has rarely been reported except following ingestion with suicidal intent, however, two young adults who ingested it with suicidal intent, developed neurological, cardiac, hepatic and renal toxicity and died (Singh et al.2003). Nair et al. (2005) demonstrated that 2, 4-D is capable of inducing higher DNA damage as well as chromosomal aberrations in human lymphocytes. Flanagan et al. (1990) reported that 6 of 30 patients who had ingested 2, 4-D formulations alone died; 16 patients (mostly in grade 3-4 coma) had alkaline diuresis and 15 survived. Singla et al. (2017) reported a 14-year-young male ingested 50ml of 2, 4-D solution became markedly restless and drowsy two hours and died on next day. Singh et al. (2003) reported two young adults who ingested 50-100 mL it with suicidal intent, developed neurological, cardiac, hepatic and renal toxicity and died 2,4-D has demonstrated toxic effects on the thyroid and gonads and showed a concern over potential endocrine-disrupting effects (Reregistration Eligibility Decision (RED) 2005).

Acute respiratory distress syndrome because of paraquat usually appears 24–48 h after ingestion (Singh et al. 1999).

Weight loss, weight changes in internal organs, reduced brain size together with lesions is reported by butachlor (Panneerselvam et al. 1999). Similar cancer is reported by atrazine (Wang et al. 2023). It is determined that butachlor can trigger a dose-dependent increase in the frequency of chromosomal aberrations in human lymphocytes (Sinha et al. 1995). Toxic effects of butachlor on human innate immune system have also been observed (Moser and Leo 2010).

In the 1990s effects of glyphosate in humans demonstrated the symptoms of acute poisoning. Gastrointestinal symptoms, respiratory distress, hypotension, altered level of consciousness, acute renal failure, extensive chemical burns, and death have also been reported (Roberts et al. 2010). Overviews on potential effects of glyphosate on human health and the environment are summarized and reported by Van Bruggen et al. 2018, Gandhi et al. 2021).

In literature, toxicity to a 25-year-old male farmer who consumed approximately 50 mL of pendimethalin 30% EC started recurrent episodes of watery vomiting, headache, burning sensation and pain in throat and abdomen within 10 & 15 minutes (Kumar & Verma 2013) and later on became drowsy followed by altered sensorium and unconsciousness is reported in India. In another case report, a 73-year-old man developed nausea, epigastric pain and corrosive gastroduodenal injury after accidental ingestion of pendimethalin (Tsukada et al. 2009).

Acceptable daily intake and LD_{50} values are predict toxicity of herbicides. For instance, the acceptable daily intake (ADI) and LD_{50} value of sulfosufuron (0.24mg/kg and 5000mg/kg) is high in comparison to butachlor, diuron, glyphosate, oxyflourfen and pendimethalin (0.01, 0.007, 0.5, 0.003, 0.125 mg/kg bw/day, respectively) that predict less health hazards by this herbicide. In contrary of the ADI of atrazine, diuron and oxyflourfen (0.02, 0.007 and 0.003 mg/kg bw/day, respectively), the potential risk of adversity to human health and other life is high in comparison to butachlor, glyphosate and sulfosulfuron. Though LD_{50} value of pendimethalin is 5000mg/kg but its ADI is 0.003 mg/kg/day which predicts a considerable risk to human health. It is also interesting to note that LD_{50} and ADI values of glyphosate is 4320 mg/kg and 0.5 mg/kg bw/day, respectively.

It is well established that the spleen is the main and secondary lymphoid organ responsible for blood formation during the early stage of life. Previously, it is recorded that brain hematoma in patients having intracerebral hemorrhage greatly impacted the spleen shrinkage (Zhang et al. 2019). There is also the possibility of venous and arterial thrombosis (Iolascon et al. 2017). Cases of acute poisoning by some of the herbicides are listed in **Table 14**.

Table 14. Reported cases of intentional herbicide poisoning in human in India

Poisoning	Total patients	Death	Amount taken (mL)	Reference
2-4 DEthyl ester	05	02	50-150	Singh et al. 2003, 2008, Kumar 2019, Rajendran et al. 2021, Tiwari et al. 2017
Atrazine	NA	NA	NA	NA
Butachlor	NA	NA	NA	NA
Diuron	NA	NA	NA	NA
Glyphosate	03	01	25-400	Das et al. 2012, Khotet al. 2019, Chakraborty et al. 2022
Oxyfluorfen	01	-	150	Selladurai Pirasath et al. 2021
Pendimethalin	04	02	20-100	Kumar & Verma 2012, 2013
Sulfosulfuron	01	-	Unknown	The New Indian Express, 2021

NA=Not Available

10. Toxicity and Adverse effect of herbicides

(i) 2, 4-D

2, 4-D (2, 4-dichlorophenoxy acetic acid) is a systemic auxin type selective herbicide and is commonly used in cereal crops. Being a polar molecule it easily reaches to water bodies. 2,4-D and its ester and amines are quite mobile in aqueous systems because of its acidic carboxyl group (pKa=2.8) and low soil adsorption, surface runoff or through infiltration, leaching and soil percolation that may be the reason for its widespread occurrence in the environment (Shareef and Shaw 2008; Islam et al. 2018). 2, 4-D is reported to be a moderately persistent in the environment with a reported half-life of 20 to 312 days (Walters 2011). Sharma et al. (2013) reported its persistence up to 15 to 75 days in wheat crop at 0.5 to 2.0 kg/ha with the half-life from 4.21-17.70 days. Residues of 2, 4-D were found below detectable level (0.02 ppm) in wheat grain and wheat straw. 2, 4-D leached in coarse textured low organic matter soil (Mannuthy–Ultisol) upto 60 cm depth. Oxyfluorfen residues were not detected in the leachate (Durga et al. 2015). Xiang et al. (2018)reported that butachlor (1-15 µmol/L) significantly increased the mortality and malformation rates in a dose-dependent manner in zebrafish, which caused elevation in reactive oxygen species (ROS) and malondialdehyde (MDA) after 72 h exposure. Stockley et al (2006) reported 2,4-D greater than the limit of quantification (1 µg/L) and the highest concentration was found to be 2.9 µg/L in seven wine sample of Australia, 44 wine samples (approximately 43%) contained a concentration of 2,4-D greater than the limit of detection (0.5 µg/L).

2, 4-D was categorized as Group D - not classifiable as to human carcinogenicity in 2004 (Reregistration Eligibility Decision (RED) 2005). The International Agency for Research on Cancer (IARC), had not assigned 2,4-D a cancer rating as of June 2008. However, in 1987, IARC placed the family of chlorophenoxy herbicides in Group 2B, possibly carcinogenic to humans (IARC 1987). Metabolism of 2, 4-D is reported minimal in humans and nearly all of it excreted unchanged as the parent compound (Munro et al 1992). 2,4-D is included in the U.S. EPA June 2007 Draft List of Chemicals for Tier 1 Screening (Draft List of Initial Pesticide Active Ingredients and Pesticide 2007). Rabbit fetuses were unaffected at doses below 40 mg/kg/day administered to the dams although extra ribs were formed at doses above this threshold. In rabbits, the developmental NOEL was 30 mg/kg/day 2,4-D acid equivalents (Charles et al 2001).

Residues of 2,4-D were detected in 49.3% of finished drinking water samples and 53.7% of untreated water samples (365 and 367 samples), with detections between 1.1 and 2416.0 parts per trillion (ppt) (Pesticide Data Program Annual Summary, Calendar Year 2006 2002). In bottled water, 2 of 367 samples contained 2,4-D, with residues of 3.2 and 4.2 ppt. Toxicity of 2,4-D to fish and aquatic invertebrates varies widely depending on chemical form, with esters being the most toxic (Tomlin 2006). Acid and amine salt LC_{50}s range from greater than 80 to 2244 mg acid equivalents per liter (mg ae/L) whereas the esters range from less than 1.0 to 14.5 mg acid equivalents per liter. The greater toxicity of the esters in fish due to the greater absorption rates through the gills, where they are hydrolyzed to the acid form. The acute LC_{50} of the dimethyl amine salt form to rainbow trout was 100 mg/L, which is considered slightly toxic (Tomlin 2006). The MCL for 2, 4-D in drinking water is 0.07 mg/L (Drinking Water Contaminants 2008). The sensitivity of aquatic invertebrates to 2, 4-D increases with temperature. 2, 4-D has been detected in streams and shallow groundwater at low concentrations, in rural and urban areas (Reregistration Eligibility Decision (RED 2005).Volatility for most forms of 2, 4-D is reported to be low. However, the vapor pressure of some ester forms range from 1.1×10^{-3} to 2.3×10^{-3} mmHg indicating that these forms readily volatilize. The Henry's Law Constant for 2, 4-D acid is 3.5×10^{-4} at pH 7, indicating low potential for movement from water to air.

(ii) Atrazine

Atrazine is a synthetic triazine herbicide used to control grassy and broadleaf weeds in sugarcane, wheat, conifers, sorghum, nuts and corn crops (Zhao et al. 2017). Atrazine does not bind well to soil and has long half-life of 41–231 days (Karlsson et al.2020). Due to low adsorption in soils and moderate water solubility, it has a potential to contaminate ground and surface water (Kumar et al. 2013,Sondhia 2014, 2018). Atrazine degrades slowly by water, sunlight, and microorganisms (Draft Human Health Risk Assessment for Registration Review 2018). It degrades more slowly in less acidic soil. Atrazine may be more persistent in colder climates in aquatic organism such as fish, amphibians, aquatic plants, and aquatic invertebrates, the breakdown products of atrazine were less toxic than atrazine. Breakdown products of atrazine were found to be equally or slightly more toxic to birds and mammals. (Refined Ecological Risk Assessment for Atrazine 2016). Atrazine was banned in several countries like Italy, Denmark, Finland and Germany (Vonberg et al. 2014) in the year 1991 and European Union banned atrazine in the year 1992 (Atrazine was banned in the European Union (EU) in 2003 and it is classified as an endocrine disrupting herbicide by the US Environmental Protection Agency. The International Agency for Research on Cancer (IARC) has categorized atrazine in the list of carcinogenic herbicide (Mahler et al. 2017).

Duttagupta et al. (2020) reported atrazine (0.95–3.93 µg/L) residues 46 times higher than the permissible limits in Ganga River (32 locations) and ground water (233 locations) in west Bengal. Aslamet al (2013) detected atrazine in 45% ground water samples of Delhi with the total mean concentrations ranged from 0.00072 to 0.0173 mg/L and 35 % samples exceeded the WHO (0.002 mg/L) and USEPA (0.003 mg/L) limits. Sharma et al. (2016) reported below detectable levels (0.05 µg/g) atrazine residues in soil and potato tubers at the time of harvest at 0.5 to 2.0 kg/ha. Almeidaet al. (2019) reported a 2.00 µg/L atrazine and diuron residues at 12.59 µg/L in Brazil (Sposito et al. 2018). Bagwasi et al.(2021) reported atrazine persistence in the sandy clay loam soil upto 110 days with half-life of 7.68 to 24.88 days. Tandon and Singh (2015)have reported atrazine half-life of 16.4 days (soil pH 8.70) under application rate of 2 kg/ha under subtropical conditions in winter maize.

Yadav et al. (2021) reported mobility of atrazine and its metabolites, hydroxyatrazine, deethylatrazine and deisopropyl atrazine in the sandy loam soil and the clay loam soils. Nag and Das (2009) reported residues of atrazine residues in plant foliage at harvest at 1.5 kg/ha with a half-life of 10.27 -9.38 days. Atrazine and its metabolites can persist in water and soil for decades. Even more than 18 years after it was banned in Germany, atrazine remains the most abundant herbicide in groundwater samples (LAWA 2003). Gushit et al. (2012) reported atrazine (0.123-0.180 mg/kg), 2, 4-D (0.013 to 0.030 mg/kg), and pendimethalin (0.020 to 0.010 mg/kg) residues in fadama soils. Jablonowski et al. (2009) reported persistence of atrazine 22 years after the last atrazine application in a long-term outdoor lysimeter experiment with a disturbed soil column using radiolabeling.

Alice et al. (2019) reported atrazine (0.1- 8.78 mg/kg), and butachlor (0.00-0.911 mg/kg) residues in three organs of cattle (heart, liver and kidney) in Nigeria. Some of the samples recorded residue above the Maximum Residue Limits (MRLs) and that consumption of cattle organs meat might be threatening to human health. Pathak and Dikshit (2011) predicted a carcinogen potential of atrazine due to negative impact on human health such as tumors, breast, ovarian, and uterine cancers as well as leukemia and lymphoma. Atrazine impairs the fertilization of sperm by interrupting sperm plasma membrane integrity, interfering with reproduction (Tongo and Ezemonye 2015, Komsky-Elbaz and Roth 2017).

On-Anong Phewnil et al. (2012) reported 0.7 µg/L and 27.42 µg/kg atrazine in stream water and sediment samples after application in maize at 1.25-1.56 kg/ha. Atrazine residues in stream sediment is reported to be 5.87-fold significantly higher than that in the stream water. Mohamed Abuzeid et al. (2022) reportedatrazine in water samples in 26 sites in El-Behera in the range of (3.125µg/L) from Kafr El-Dawwar and Hosh Essa had the greatest residue of atrazine (109.18 µg/L). Fayinminnuet al. (2017) reported 9.98 mg/kg of atrazine residues in Irish potato varieties. The Yellow variety from both Jos South and Bokkos had the highest values of 3.32 and 3.13 mg/kg atrazine residues, while 1.51 mg/kg was found in Diamant variety in Bokkos which was above maximum residue limit (MRL) of 0.05 mg/kg and 0.1 mg/kg. Gasic et al. (2002) reported atrazine residues in soil (0–15 and 15–30 cm depth) and groundwater from 0.02 to 0.10 mg/kg (0–15 cm) and up to 0.05 mg/kg (15–30 cm). In surface and ground water atrazine residues ranged from 1.0 to 4.13 mg/L.

Kookana Rai et al.(2010) reported atrazine and one of its metabolites (DEA) at a depth after 1.8 months with half-life in surface soils ranged from 11 to 21 days and demonstrated that while its 50% (DT_{50}) loss occurred relatively rapidly (36 days), more than 10% of herbicide residues were still detectable in the profile even a year after application (DT_{90} = 375 days). Yuan et al. (2021) reported atrazine residues in 43.1% soil samples which were higher than 0.11 mg/kg, however, the final residues of atrazine in soil samples were <0.01–9.2 mg/kg. Mengjie et al. (2017) detected 171 and 0.114 mg/kg, atrazine accumulation capability in six eutrophic lakes in Hubei Province of central China sediments. Sun et al. (2017) reported atrazine residues in the agricultural soils ranged from <1.0 to 113 ng/g dry weight, with a mean of 5.7 ng/g, and a detection rate of 57.7 % in soils. The concentrations and detection rates of atrazine were higher in corn fields and mulberry fields than in rice paddy fields.

Atrazine reported to exhibit significant rate of micronuclei and nuclear abnormalities in *Channa punctatus* (Nwani et al.2011) and showed acute toxicity to leopard frog (*Rana pipiens*), American toad (*Bufo americanus*), rainbowtrout (*Onchorhynchus mykiss*) and channel catfish (*Ictalurus punctatus*) (Orton et al. 2006). Increase in lipid peroxidation and decline in cholesterol and total proteins in liver and muscles were reported by atrazine and glyphosate in tadpoles of *Lithobates catesbeianus* (Dornelles and Oliveira 2014) and decline in levels of total protein and serum albumin in grass carp, *Ctenopharyngodon idella*and on earthworms, *Nsukkadrilus mbae*is reported by Khan et al. (2016) at various concentrations of atrazine. Detrimental effects of atrazine on the digestive gland of Crassostreagigas, pacific oyster, significant decrease in hematological parameters like hemoglobin, hematocrit and RBCs due to chronic toxicity of atrazine in fish Zadeh et al. (2016) is reported.

The main target of atrazine on humans and mammals is the disruption of the endocrine system (Kroon et al. 2014). Secondly, it also induces oxidative stress by formation of reactive oxygen species causing reduced semen quality sperm dysfunction and infertility on amphibians, rats and pigs (Gely-Pernot et al. 2015), fish (Owolabi and Omotosho 2017), crustaceans (Silveyra et al. 2022) and chironomid larvae (Londoño et al. 2004) and cause single- and double-strand breaks in DNA and therefore is genotoxic (Yang et al.2010). The working of cardiovascular system also gets affected by atrazine exposure (Pereira de Albuquerque et al. 2020).

A uniform limit of 0.1 µg/L of the pesticide residue was established for drinking water and groundwater (Ackerman 2007). In 2018 draft assessment, the USEPA concluded that exposure to atrazine from food, drinking water, and residential uses poses reproductive and developmental risks to humans, particularly children (US Environmental Protection Agency 2018). In the Pampean plain, bioaccumulation of atrazine in groundwater and bovine milk in 18 dairy farms and in 44.4% of the groundwater and 11.1 % of the bovine milk samples (n=18) exceeded the safe limits for human consumption is reported. Atrazine was quantified in 50 % of the groundwater samples (0.07 to 1.40 µg/L), and in 89 % of the bovine milk samples (2.51 to 20.97 µg/L)(Urseler et al 2022). Aizhen Wang et al. (2020) reported frequent detection of atrazine and its metabolite (hydroxyatrazine; deethylatrazine, deisopropylatrazine and deethyldeisopropyl atrazine) with a detection frequency of 99.5 to 98.0% (0.44 to 706.0 ng/g) in China in tap water from 31 provinces in 7 regions of mainland China and Hong Kong during June 2019 with the highest estimated daily intake of 248 ng/kg-body weight/day was found in the infant population of Changchun, Jilin, Northeastern China. Xieet al. (2021) reported high concentrations of atrazine (> 30 ppb) in surface water and deep wells in agricultural regions of the U.S., such as Indiana, Ohio and California. Folarin Owagboriaye et al. (2017) reported 0.01 to 0.08 mg/L atrazine residue in 69 hand-dug wells (HDW), 40 boreholes (BH) and 4 major streams from all the 6 communities in Southwest Nigeria.

Exposed rats exhibited reductions in spatial learning and memory capacity as well as locomotor activities is reported by Walters, Lansdell et al. (2015). In zebrafish, embryonic exposure to atrazine caused significant changes in genes associated with movement disorders, i.e., AQP1, CDK5 and TNNI2 that are associated with dopaminergic systems (Horzmannet al. 2020). Exposure to atarzine does not only affect the exposed generation, but also its progeny (McBirney et al. 2017). Exposure to atrazine alter epigenome and epigenetic enzyme activity. In the transgenerational mice study, atrazine-exposed mice showed persistent alterations in DNA methylation and H3K4me3 that last to the third generation (F3) (Hao et al. 2016, Mc Birneyet al. 2017). Similar increase in the transcription of SNCA was reported in rats exposed to atrazine of 25 or 50 mg / (kg body weight) per day for 3 months (Li, Jiang et al. 2019). Zhuet al. (2021) reported that exposure to atrazine was significantly associated with decreased testosterone production (SMD = − 0.90, 95% CI − 1.27 to − 0.53), and reduced absolute weights of testis (SMD = − 0.41, 95% CI − 0.61 to − 0.22) and other reproductive organs.

Victor et al. (2022) reported atrazine toxicity and the binding of atrazine to human serum albumin and determine the most likely binding sites of atrazine to human serum albumin binding site FA8 (located between subdomains IA-IB-IIA and

IIB-IIIA-IIIB). Wenqi Shan et al. (2021) demonstrated that atrazine inhibited the proliferation of human embryonic stem cells (hESC) and NSC, and showed different toxic sensitivity on these two kinds of cells. Altered genes expression levels of *PAX6*, *TUBB3*, *NCAM1*, *GFAP*, *TH*, *NR4A1*, and *GRIA1* is reported by atrazine along with dopaminergic system neurotoxicity, glutamatergic neurons and astrocytes. Irregular menstrual periods in women living in areas in Illinois where atrazine is heavily used is reported. Atrazine concentration was in the residential water was 0.4 µg/L in Vermont 0.7 µg/L in Illinois (Cragin 2011). Higher risk of end-stage renal disease (kidney failure) in people is reported who had been exposed to more atrazine (Lebov et al. 2016). Exposure to atrazine, particularly in agriculture workers has been associated with increased risk of various diseases, including breast cancers (Simpkinset al. 2011), reproductive and endocrine diseases (Mungeret al. 1997), and neurodegenerative diseases (Songet al. 2015). The adverse effects of metabolites of atrazine on the immune system, central nervous system and cardiovascular function (Jin et al. 2010), and on adult humans, non-Hodgkin's lymphoma associates with the exposure of the atrazine (Schroeder et al. 2001) is reported. Peighambar Zadeh et al. (2011) reported the mean concentration of atrazine in human serum and urine samples in the range of 0.739-0.567 ppm and 1.389- 0.633 ppm, respectively. Dana et al. (2007) detected high amounts of atrazine residues in urine of farmers with their spouses and children after atrazine application on fields. GHS hazard classification for atrazine is H317 show that it may cause an allergic skin reaction; H373 - May cause damage to organs through prolonged or repeated exposure; H410 - Very toxic to aquatic life with long lasting effects; Precautionary Statements P102 - Keep out of reach of children with precautionary codes P260, P280 , P302 + P352 , P501.

(iii) Butachlor

Butachlor vapor pressure of $2.90x10^{-6}$ mm Hg at 25°C (**Table 15**) indicates that it may exist in both the vapor and particulate phases. In soil, butachlor have less mobility. Half-lives for butachlor in soil reported to be 1.6 days to 30 days. Christopher et al. (2013) reported acute toxicity of butachlor on *Tilapia zillii*. The 24, 48, 72 and 96 h LC_{50} values (with 95% confidence limits) were reported to be 3.13 (2.88 to 4.61), 1.93 (0.63 to 4.41), 1.27 (0.59 to1.92) and 1.25 (0.60 to1.85) mgl/L, respectively. Half-life of 8.5 to 29.79 days were reported in rice soil (Rao et al 2012, Janaki et al. 2016, Kaur et al. 2017). The residues of butachlor in soil, rice grain and straw samples at harvest were below the 0.001 µg/g (Sachan et al. (2007). However, Zakari Mohammed et al. (2020) reported butachlor residues significantly higher than the WHO and FAO maximum residue limits (MRLs) in the rice samples and acceptable daily intake values (ADIs).

Table 15. Physico-chemical properties of listed herbicides

Herbicide	2,4-D			Atrazine	Butachlor	Diuron	Glyphosate	Oxyfluorfen	Pendimethalin	sulfosulfuron
	Sodium salt	Amine Salt (DEA)	Ethyl Ester							
IUPAC name	Sodium 2,4-dichlorophenoxyacetate)	dimethylamine (2,4-dichlorophenoxy) acetate	Ethyl (2,4-dichlorophenoxy) acetate	6-chloro-N_2-ethyl-N4 -isopropyl-1,3,5-triazine-2,4-diamine	N-butoxymethyl-2-chloro-2',6'-diethylacetanilide	3-(3,4-Dichlorophenyl)-1,1-dimethylurea	Glyphosate N-(phosphonomethyl) glycine	-chloro-α,α,α-trifluoro-p-tolyl 3-ethoxy-4-nitrophenyl ether	3,4-dimethyl-2,6-dinitro-*N*-pentan-3-ylaniline	1-(4,6-dimethoxypyrimidin-2-yl)-3-(2-ethylsulfonylimidazo[1,2-a]pyridin-3-yl)sulfonylurea
Molecular weight g/mole	243.03	266.13	249	215.68	311.8	233.09	169.07	361.70	281.31	470.5
Molecular Formula	$C_8H_5Cl_2NaO_3$	$C_{10}H_{13}Cl_2NO_3$	$C_{10}H_{10}Cl_2O_3$	$C_8H_{14}ClN_5$	$C_{17}H_{26}ClNO_2$	$C_9H_{10}Cl_2N_2O$	$C_3H_8NO_5P$	$C_{15}H_{11}ClF_3NO_4$	$C_{13}H_{19}N_3O_4$	$C_{16}H_{18}N_6O_7S_2$
Solubility in water (g/L)	45	320-664	-	0.70	0.020	0.42	10.5	0.116	0.33	17.6
pH	-	6.8 -9	-	2.7	-	-	2.7	-	-	-
Pka	-	-	-	-	16.6	13.55	-	-	-	3.51
Vapour pressure (mPa)	0.0187	9.98×10^{-8} mmHg	-	$4x17^{-5}$	0.254	1.15×10^{-3}	0.0131	0.026	1.94	3.05×10^{-8}
Henary Law constant (Pa m^2mol^{-1})	3.10×10^{-3}	-	-	1.50×10^{-4}	3.74×10^{-3}	2.06×10^{-6}	2.10×10^{-7}	0.02382	2.73×10^{-3}	8.15×10^{-7}
Melting point (°C)	215	118–120	-	173-175	-2.8	157	189.5	85.3	58	201
***Log K_{ow}**	2.14 to 0.102	2.24×10^{-2} -1.65	-	2.61	4.51	2.87	-3.20	4.73	5.20	0.73-1.44
Koc	20-136			50-109.9	700-6700	62.6-2.9	2500-4900	0.315 ug/L	7,011-43,863	
Ld_{50} oral (mg/kg) (Rat)	375 to 666			672	1740	1017	4320	5000	1250	5000
Reference Dose (RfD) mg/kg/day	0.01			0.1	-	0.016	0.5	0.3	0.13	0.24
ADI (mg/kg bw/day)	-			0.02	0.01#	0.007	0.5	0.003	0.125	0.24
Hazard (toxicity)** rating	II			III	III	III	III	III	III	IV
Signal	Caution to Danger			Warning	Danger	Warning	Danger	Warning	Warning	Warning

*https://pubchem.ncbi.nlm.nih.gov/compound/; Toxicity based on LD50 value (mg/kg); 0-50 (I) High Toxicity; 50-500 (II) Moderate Toxicity; 500-5000 (III) Low toxicity; <5000 (IIII) very Low toxicity

Butachlor causes slight erythema and edema in rabbits when exposed to 24 h and on a scale of 8.0, and a primary irritation index of 3.5 is reported (Wilson and Takei 2000). It was also found to cause primary ocular irritation in 2 of 6 white rabbits tested. The guinea pigs, when challenged with 50 % butachlor, moderate-to-severe erythema with edema were noticed on the third application. Adverse effects of butachlor on the growth, nitrogen fixation and photosynthesis of many cyanobacterial species viz. *Anabaena doliolum* and Nostoc is reported (He et al. 2013). Butachlor at recommended field dose is reported to affect the lipid synthesis of leaf cells of *Phaseolus vulgaris* L. plants and alleviates the glutathione and its associated enzymes in butachlor tolerant plants and its application at recommended field dose resulted in differentially less shoot fresh and dry weight after about 16 days of exposure in the *Phaseolus vulgaris* L. Pan et al. (2009) reported adverse effect of butachlor on chlorophyll a content and relative growth rate on three submerged macrophytes (*Ceratophyllum demersum*, Vallisnerianatans and *Elodea nuttallii)* at a lower concentration (0.0001 mg/L).

Butachlor hinder the synthesis of very long-chain fatty acids of a fresh water cladoceran *Daphnia carinata* (He et al. 2013) and shown to be genotoxic and cytotoxic in catfish *Clarias batrachus*, and caused DNA damage (Zheng et al. 2012). Remarkable protein loss in *C. batrachus* at lethal and sub-lethal concentration is reported by butachlor (Rajput et al. 2012). Butachlor caused adverse effects on the normal reproductive process of zebra fish and disrupt the thyroid and sex steroid endocrine systems when exposed for 30 days (Chang et al. 2013). The accumulated residues in different tissues of the fish, resulted in bio-magnification of butachlor *via* the food chain (Tilak et al. 2007). An increased malondialdehyde formation, glutathione level, glutathione-S-transferase activity, superoxide dismutase and catalase activity (Coleman et al. 2000, Ou et al. 2000), the biological and biochemical toxicity on freshwater snails *viz*. *Pila globosa* and *Biomphalaria alexandrina* (Tantawy 2002) and the inhibition of ATP were reported by the toxicity of butachlor to flatfish.

Butachlor detrimental effects on earthworms (Dwivedi et al. 2012), mutagenic effects in primary rat tracheal epithelial cells and in Chinese hamster ovarian cells (Hill et al. 1997) and stomach tumors in rats (Xu et al. 2007a) are reported. On prolonged exposure, it was found to be toxic to spotted snakehead fish (*Channapunctata*) and also accumulates *via* the food chain (Tilaket al. 2007). Butachlor has been reported to be a neurotoxin to land snails and as a genotoxin to catfish, toads, flounder, and frog tadpoles (Ateeq et al. 2005, Geng et al. 2005), *P. megacephalus* and *Bufo gargarizans* (Liu et al. 2011) and indirect mutagen to hamsters and rats (Hsu et al. 2005) and negative impacts on the amphibians present in the paddy field (Liuet al. 2011). Dwivedi et al. (2012) reported associated risks of butachlor to humans in human peripheral blood mononuclear cells (PBMN) due to their oxidative role in intracellular reactive oxygen species (ROS) production, and the consequent mitochondrial dysfunction, oxidative DNA damage and chromosomal breakage. Butachlor exposed cultured mammalian cells exhibited DNA strand breaks and chromosomal aberrations (Pan-neerselvam et al. 1999).

The concentration of 0.911 ppm butachlor were detected in Abbatoir market. Ying et al. (2009) detected butachlor in animals after consumption of contaminated water. Also butachlor residues ranged from 0.0012 to 0.0014 µg/g in fish tissues from different markets in India (Choudhury 2013) is reported. Gobi and Gunasekaran (2010) reported effect of exposure to butachlor on biomass, clitellum development, and cocoon production and the histological changes in the earthworm *Eisenia fetida* over 60 days, the dried cow dung was contaminated with 0.257, 0.515, and 2.57 mg/kg of butachlor residues and reported butachlor 96 h LC_{50} of 0.515 mg/kg for *Eisenia fietida* and 0.163 ppb butachlor residues in ground water in tube wells adjacent to rice fields in Philippines (Natarajan 1993). Yadav et al. (2010) reported genotoxic effects of sublethal concentration of butachloron Indian major carp *C. mrigala* at 1.0 kg/ha dose for 24, 48, 72 and 96 hexposure. Broken Egg (BE) and multiple micronuclei appeared after 72 and 96 h, respectively and significantly ($p<0.05$) low accumulation of carcass protein, muscle glycogen levels were observed. Gill et al. (2020) reported butachlor residues in rice grains and rice straws. In Bhubaneswar, among 205 milk samples, two samples were detected 0.1-8.78 ppm atrazine residues while 0-0.911 ppm butachlor residues were reported in three market samples. The concentration of atrazine residues in cattle organs were high exceeding the 0.05 ppm maximum residue limits by WHO/FAO. Atrazine residues were detected in all the markets.

Butachlor metabolism in rats follows three major pathways: initial conjugation with glutathione (via glutathione S-transferases) followed by mercapturic acid pathway metabolism; cytochrome P-450-mediated hydroxylation of the aromatic ring, its ethyl groups and the N- butoxymethylene group; and cleavage of the amide bonds via aryl amidase to form 2,6-diethyl aniline, which is further oxidized to 4-amino-3,5-diethylphenol. (T80, A572) (Toxin and Toxin Target Database (T3DB). Globally Harmonized System hazard identification code for butachlor is H331 (39.36%): and showed toxic if inhaled (Danger, Acute toxicity, inhalation). Butachlor binds to nAChRs in nervous systems. It causes endocrine disruption in humans by binding to and inhibiting the estrogen receptor. (T10, A590) (Toxin and Toxin Target Database (T3DB)). The potential for toxic effect in the occupational setting is based on cases of poisoning by human ingestion or animal experimentation are reported (Haz-Map, Information on Hazardous Chemicals and Occupational Diseases, https://haz-map.com/ Agents/4023).

(iv) Diuron

Diuron 3-(3,4-dichlorophenyl)-1,1-dimethylurea) has been registered and for used for weed management in several many countries to control germinating grass and broad-leaved weeds in many crops, including fruit trees, vines, cereals and sugar cane and mosses in non-crop areas. Diuron, is an herbicide of urea chemical family that inhibits photosynthesis and introduced by Bayer in 1954. Diuron sorption is highly correlated with organic matter (Spurlock and Biggar 1994). Leaching is high in low organic matter soils, it exhibits low solubility in water **(Table 15)**. Due to the diuron's persistence and mobility, it is one of the most frequently detected herbicide in California's ground water (Troiano et al., 2001). Kaonga et al. (2015) reported 65 ng/L diuron residues in surface and bottom water. Microbial degradation is reported to be the primary means of diuron dissipation from soil. In plants, diuron is metabolized *via*

N-demethylation. Diuron was metabolized to conjugates of monomethyl diuron which is a biologically active pollutant present in soil, water and sediments. Diuron is reported to be persistent in soil, water and groundwater. It is also slightly toxic to mammals and birds as well as moderately toxic to aquatic invertebrates. However, its principal biodegradation product, 3, 4-dichloroaniline exhibits a higher toxicity and is also persistent in soil, water and groundwater (Directive 200/60/CE) (Bayer 1998). Organic matter (OM), pH and clay content, as well as the base saturation of the soil, are the attributes with the most significant influence on the sorption and desorption of diuron. Degradation by microorganisms is the primary means of diuron dissipation in soil (Rodrigues et al. 2018). Half-life of 15-81 (Silva et al. 2019) is reported for diuron in soil. The percentage of the extractable residue of diuron was higher (~38%) in the sandy soil than in the clay soil (~ 30%) regardless of how it was applied (mixture or alone). Diuron had the highest percentage of bound residue (Reis et al. 2023).

Adejoro et al. (2019) suggested that sensitive vegetables such as *C. olitorius* should not be sown as successive crop in which diuron had been applied to control weeds at the usual recommended rate of 3.0 kg/ha. Diuron is prohibited in France since 2008 as a phytosanitary substance and as a biocide since 2009 (Directive 2008/91/EC). Diuron is not well degraded naturally (Tixier et al. 2001) and still detected at high concentrations in French coastal and fresh waters (Caquet et al. 2013) and considered as a potential Persistent Organic Pollutants (POP) (Scheringer M et al. 2012). However, it has been reviewed in the United States (draft 2003), Canada (2007), United Kingdom (2007) and Europe (2007 and 2008). Restrictions on the use of diuron in these jurisdictions have been implemented (reductions in frequency and rate of application and restrictions on crop uses) with a view to protecting aquatic environments in 2005 (apvma.gov.au). Safiatou and Boua Célestin Atse (2019) detected diuron from 0.09 to 2.42 µg/kg in Côte d'Ivoire and the level of diuron contamination in water, sediment and farmed fish. Diuron was detected in water (11%) and fish (16%). Trovato et al. (2018) reported 637 (± 50) µg/L diuron residues as runoff from a soil with different levels of sugarcane straw coverage in Brazil where diuron was applied at 3.2 kg/ha in sugarcane.

Diuron is reported to be carcinogenic to the rat urinary bladder at high dietary levels with mode of action urothelial cytotoxicity and necrosis followed by regenerative urothelial hyperplasia. Diuron is extensively metabolized, and in rats, N-(3, 4-dichlorophenyl) urea and 4, 5-dichloro-2-hydroxyphenyl urea were the predominant urinary metabolites; lesser metabolites included N-(3, 4-dichlorophenyl)-3-methylurea and trace levels of 3, 4-dichloroaniline. In humans, N-(3, 4-dichlorophenyl)-3-methylurea and N-(3-4-dichlorophenyl) urea have been found in the urine (Da Rocha et al.2013). Diuron has known human metabolites that include N-demethyldiuron .Diuron concentrations (381ng/Lto 83 ng/L) is reported in water (Extension Toxicology Network 1993). Diuron and its derivatives has half-life of 1-12 months and 1-5 months, respectively and in pineapple farms, diuron persistence for three years after the application is reported (Extension Toxicology Network 1993). In Georgia, Sope Creek and the Chattahoochee River, diuron and 3, 4-dichloroaniline (3, 4-DCA) were detected in 100 and 80%, respectively, of the samples from the Chattahoochee River, whereas Sope creek had detection frequencies of 15% for diuron and 31 % for 3, 4-DCA (Hladik and Calhoun 2012).

Sharma et al. (2019) detected diuron, 2, 4-D and atrazine and its degraded products (desethyl-atrazine and desisopropyl-atrazine) in local waterways draining from sugarcane industry into the downstream of wetlands and diuron being the most abundant herbicide in terms of occurrence (Stork et al. 2008). Acayaba et al. (2021) also reported 2-hydroxy atrazine, diuron, as the most frequently detected at the highest concentrations in surface and groundwater in the region (100, 94, %, respectively) with the largest sugar cane production in the world. Similarly, diuron was dominantly found in inter- and sub-tidal deposits of Great Barrier Reef (Duke et al. 2005). In Melbourne, Australia, Allinson et al. (2017) reported diuron (63%) and atrazine (53%) in five different aquatic systems in high concentrations. In most of the studies conducted in North America, glyphosate (Howe et al. 2004) and atrazine (Solomon et al. 2013) are the two commonly found herbicides in water bodies.

Richards et al. (2023) reported detection frequency of >70% of atrazine, atrazine-desethyl, and diuron in surface water along a ~ 500 km segment of the iconic River Ganga. García-Valverde et al. (2023) reported diuron in 6 (out of 8) in wastewater (raw and treated) as well as in river water and coastal water with an average concentration levels of 0.16 and 0.3 µg/L. Diuron was found in coastal water (average concentration 2.2 ng/L) and rive water (average concentration 5.2 ng/ L1). Among 80 chemical pollutants detected in 27 sampling points from Beijing and Tianjin, diuron residues were higher than the maximum residue limit of EU drinking water (0.1 mg/L) (Konget al.2016).

Diuron significantly induced the production of reactive oxygen species (ROS) during the first 21 days of exposure at 0.05, 0.5, and 5.0 mg/kg soil concentration on earthworm *Eisenia fetida* and low damage of coelomocyte DNA in *Eisenia fetida*, while no tissue damage was observed on days 7 and 14 (Wang et al.2022). Diuron and its metabolites impaired ATP levels and a decrease in the survival in *Caenorhabditis elegans* L1 larval stage at a concentration of 0.5 to 500 µM and demonstrated an alteration in mitochondrial function apart from dopaminergic neurotoxicity and induced alterations in the worms' locomotor behavior Lima et al. (2022). Velki et al. (2019) reported inhibition in acetylcholinesterase activity, gene expression and activities of some of the cytochrome P450 family enzymes on zebrafish larva by diuron. Diuron metabolized in *Torilis arvenis* and to N-dealkylated derivatives in *Lolium rigidum*. Ibrahim et al. (2020) reported hormetic developmental deformities in embryo-larvae of *Javanese medaka* fish at 5 mg/L and 10 mg/L exposed groups. Njoku et al. (2017) reported residues above the MRL (diuron and atrazine residues 0.231 and 0.093 mg/kg) in *T. occidentalis* collected from Oyingbo market. Akchaet al. (2021) reported genetic and epigenetic effects of diuron in oyster genitors *Crassostrea gigas*at environmentally realistic concentrations of 0.2–0.3 µg /L during two 7-day periods at half-course and end of gametogenesis. Diuron exposure was shown to decrease global DNA methylation and total methyltransferase activity that significant decrease in DNMT1 gene expression indicated a complex interaction between DNA damage and DNA methylation. Hypermethylation was detected in the digestive gland, whereas diuron exposure had no effect on gill and gonad tissue.

Rondon et al. (2016) reported genotoxic effect of diuron in Pacific oyster. Further, in the offspring, a RNA-seq analysis demonstrated significant change in the transcriptional profile on F1 spat that could explain developmental and growth impairment observed in F1 early life stages. Diuron-supplemented sediments triggered the significant decrease of meiofaunal abundance as well as a change in nematodes' diversity and structure composition at concentrations of 10 ng/g to 1250 ng/g DW compared to non-contaminated sediments (controls) for 30 days (Hannachi et al. (2022). Diuron toxic effects on zebrafish embryos, aquatic invertebrates, bees and algae are reported by Shao et al. (2023). Siviter et al. (2023) detected atrazine (3.3 %) and diuron in 322 bees (181 samples, from 8 genera) across 10 sites with the highest concentrations (1.9 ppb) of diuron residues. Cui et al. (2022) predicted toxic global ecological risk and 2.54%-14.4% species in the common case, and impact 7.08%-48.1% species in the worst case are expected to be affected by the six herbicides based on the concentration and toxicity data.

Diuron posed high risk to Spain and Italy. Mohamat et al. (2021) reported toxic effect of diuron on *Tegillarca granosa* at 48-h exposure in different concentrations (0, 1, 2, 3, and 4 mg/L) and1.27–8.09 mg/kg, w/w diuron residues in the soft tissue of *T. granosa* were reported. The mean index values of the gill histopathology ranged from 5.25–7.67 and classified as moderate to severe. Kamarudin et al. (2020) reported toxicity of diuron on 210 numbers adult *Javanese medaka*, fish exposed at concentration of 1.0 to 1000 µg/L for 21 days. Diuron caused histopathological alterations in gonads (ovary and testis) of Javanese medaka (*Oryzias javanicus*) by decreasing in gonadal staging and maturity of germ cells in oogenesis and spermatogenesis of female and male. Mohamat-Yusuff et al. (2021) reported impact of diuron contamination on blood cockles (*Tegillarca granosa*) in a combining field screening at three sampling events and a toxicity test under a 72-h exposure. Diuron residues in water samples after the irrigation water discharged from the paddy plant were reported upto 3910 ppb. Mortality of *T. granosa* ranged from 4.74 to 38.33% with the LC_{50} value of 1.84 ppm. Mohamat-Yusuff et al. (2021) reported abnormal behavior on chicken received 5 µg/g and above diuron. A reduction in growth weight and enlargements in the liver and heart, inhibition on serum ACHE were observed in chicken received a single repeated dose of diuron. Jonsson et al. (2019) reported the mean values of bioconcentration factors 4.783 for diuron as a results of intensive herbicide use in the sugarcane industry and residues in the muscle tissue of tilapia (*Oreochromis niloticus*). Diuron, DCPMU and DCA also decreased the multixenobiotic resistance (MXR) activity. Nahhal et al. (2020) reported significantly reduction in the body, liver and heart weight and reduced the serum AChE, AST and ALT activities, creatinine concentration in the blood serum and increased ALP activity compared with those of the control group (p = 0.045 due to diuron concentrations below maximum residue limit (MRL) in rabbits.

Lagunas-Basave et al. (2022) reported 5.77 and 402 ng/L residues of atrazine and diuron in surface and well water due to agriculture activity in México. Britto et al. (2012) reported 0.9 µg/L diuron residues in the Poxim River of Sergipe. Orlando et al. (2014) detected diuron in 72% of the Sacramento-San Joaquin River delta surface water samples in California, with a maximum detected concentration of 0.695 µg/L. Studies have reported the killing of algae (Perschbacher and Ludwig 2004) and effects on oyster gametogenesis (Rondon et al. 2016) in the presence of diuron apart from decrease in zooplankton and micro-invertebrate species and changes in the phytoplankton community with chronic exposure to diuron (Hasenbein et al. 2017). Diuron has been detected in monitoring programs across tropical areas such as Australia, Brazil, Chile and Hawai and the deep drainage half-lives of diuron was approximately 5.25 times greater than surface runoff at Mackay-Whitsunday sugarcane sites (Davis et al. 2015).

Diuron is reported to be non-volatile due to low vapour pressure (6.90 x10^{-8} mm Hg (25^{o} C), and a low Henry's law constant (5.10 x 10-10 atm.m3/mol. Under hydrolysis control, diuron did not degrade at 25°C in the pH 7 and 9 solutions, and slightly degrades at pH 4 - 5 with half-lives of 798 and 313 days. At a higher temperature of 50°C hydrolysis occurs for pH 4, 5 and 9 with half-lives of 26, 56 and 109 days, respectively and its two degradation products N'-(3, 4-dichlorophenyl)-N-methyl urea (DCPMU) and 3,4-dichloroaniline (DCA) half-life is greater than 500 days (Kerle et al. 2015). Faizullah et al. (2020) reported persistence of diuron beyond 120 days in red and black soils with field half-life of 53.3-77.0 days when applied to cotton as preemergence spray (0.5, 0.75, 1.0 kg/ha). Tandon and Singh (2019) reported persistence of diuron for more than 100 days in sandy loam with half-life of 22.57 to 43.93 days at 2 and 4 kg/ha applications. At harvest, diuron residues were below maximum residue limits in all samples. The presence of desethyl atrazine and diuron is reported in the insects due to uptake of plants growing in areas treated with herbicides (Badanaro and Dué 2022) in *A. ruficornis* (0.320 µg/kg), and 0.640 µg/kg in *I. obscura* were detected with desethyl atrazine. While diuron has been found in *O. monoceros* (0.217 µg/kg) and *M. bellicosus* (0.532 µg/kg) in Togo country.

Diuron is moderately irritating to the eyes and slightly irritating to the skin, eye, nose and throat (Sonchieu et al. 2018). It has been reported to cause slight anemia, bone marrow changes, enlarged spleen, and abnormal blood pigments (Sonchieu et al. 2017). The US-EPA (2004) classifies diuron as a known/likely human carcinogen. Due to its harmful effects on the environment and human health its usage was restricted in the UK and EPA but it is still widely used in India and rest of the world. Impact on human hemoglobin (HHb) can be infected by diuron. Diuron induced the denaturation of Hb (Khatibi et al. 2019). Maximum diuron concentrations in water were >30 times higher than the estimated predicted no-effect concentration (PNEC) value (0.054 µg/L) indicating a risk to aquatic community. Calculated pore water concentrations (0.992–0.081 µg/L), exceeded the estimated PNEC values during the dry season, indicating a risk to benthic organisms.

(v) Glyphosate

Glyphosate is an organophosphorus broad spectrum non selective herbicide used worldwide for weed control in agriculture, mostly preplanting, as well as around roadways and railroads. The herbicidal function of glyphosate was discovered in 1970 by John Fran (2012). Glyphosate inhibits 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), an enzyme in the shikimate pathway that is required for *de novo* synthesis of aromatic amino acids in plants. Because these amino acids are necessary for synthesis of proteins and lignin in all eukaryotic plants (Tzin and Galili 2010). Recently transgenic varieties of corn, soybeans, canola, and sugar beets were made tolerant to glyphosate by the insertion of a gene that encodes for a Class II microbial EPSPS that is not inhibited by glyphosate. Aminomethyl phosphonic acid (AMPA) is a major degradation product of glyphosate (Duke et al. 2008). Metabolism of absorbed glyphosate has not been shown to occur in rats and humans (Niemann et al. 2015).

IARC classified glyphosate as Carcinogenic Classes Group 2A: Probably carcinogenic to humans. Materu et al. (2021) reported glyphosate/AMPA (0.01–0.55 µg/g) and diuron residues (0.026–1.7 µg/g) in the sediment and soils near the sugarcane farms in Tanzania. Zgheib et al. (2012) detected glyphosate with a maximum concentration of 232 µg/L in storm water runoff samples from three catchments in the Paris, France metropolitan area, collected following 20 storms. Due to glyphosate use along roads and railways a concentration range of 75-90 ug/L glyphosate residues were detected in storm sewer water, France (Botta et al. 2009). Glyphosate exposure can have sub-lethal effects on bee behaviour (Balbuena et al. 2015). In 2022, the European Chemicals Agency (ECHA) carried out a hazard assessment of glyphosate and concluded that it did not meet the scientific criteria to be classified as a carcinogenic, mutagenic or reprotoxic substance. EFSA used ECHA's hazard classification for the purposes of the EU risk assessment on glyphosate. However several unresolved issues include, a lack of information about the toxicity of one of the components present in the glyphosate-based formulation submitted for evaluation, which is needed to conclude the risk assessment of the formulation for representative uses. With respect to ecotoxicology, the data package allowed a conservative risk assessment approach, which identified a high long-term risk to mammals in 12 out of 23 proposed uses of glyphosate.

Bohn et al. (2014) reported glyphosate in organic, conventional, and GT soybeans from 31 individual fields in Iowa. In genetically modified soybean samples the average concentrations of glyphosate and AMPA were 3.26 (range = 0.4–8.8) mg/kg and 5.74 (0.7–10) mg/kg, respectively. Approximately 20% of glyphosate from diet is absorbed by the gastrointestinal tract, with the remaining being excreted to feces (Neimann et al. 2015). A pilot study conducted in 2017 detected glyphosate in 20% of the urine samples collected from Irish adults (Connolly et al. 2018). Out of the 50 samples analyzed, 10 (20%) contained detectable levels of glyphosate (0.80–1.35 µg/L). Exposure concentrations are higher than those reported in comparable studies of European and American adults. Mesnage et al. (2017) reported that glyphosate at ≥10 mg/L or 59 µM increase proliferation of estrogen-dependent MCF-7 human breast cancer cells and increase in the expression of an estrogen response element-luciferase reporter gene (ERE-luc) in T47D-KBluc cells, which was blocked by the estrogen antagonist ICI 182,780. Transcriptomics analysis of MCF-7 cells treated with glyphosate revealed changes in gene expression reflective of hormone-induced cell proliferation but did not overlap with an ERα gene expression biomarker.

Glyphosate is reported to be routinely detected in foodstuffs (Herbert et al. 2014) air and rain (Majewski et al. 2014). The reported half-life of glyphosate is variable 47 to 315 days depending on environmental conditions. Carretta et al. (2021) reported 73 µg/kg glyphosate residues in the soil at 0–5 cm at 182 days in the no tillage and 38 µg/kg in conventional tillage soil. The dissipation of AMPA was substantially slower than that of glyphosate with longer half-life (249.9 ± 27.3 and 110.0 ± 6.61 days for NT and CT, respectively). The higher glyphosate adsorption observed in no tillage causing the higher residues of glyphosate in NT than CT soil within the same depth (Piccoli et al.–2017).

A number of *in vivo* toxicity studies such as uterus, the hypothalamic–pituitary–gonadal axis, testis and ovaries (Cassault et al. 2014, Guerrero et al. 2017,) have suggested effects of glyphosate and its commercial formulations on reproductive organs . However, these studies did not clear whether toxic effects are due to endocrine disrupting mechanisms or result from a more general cytotoxicity mechanism. However glyphosate was suggested to have endocrine interference properties by inhibiting aromatase enzyme activity (Richard et al. 2005) and activating estrogen receptors (ER) (Thongprakaisang et al. 2013). Though no evidence of potential interaction of glyphosate with the estrogen pathway has been detected in the Endocrine Disruptor Screening Program (EDSP) conducted by the US Environmental Protection Agency (US EPA 2015). Mesnage et al. (2013) mentioned that glyphosate cannot be used for weed control without formulation product and commercial formulations can be up to 1000 times more toxic than glyphosate in human cell lines due to surfactant-mediated cell membrane disruption, with POEA being ~10,000 times more toxic than glyphosate alone.

Although, Gasnier et al. (2009) reported endocrine-disrupting effects on human liver cell lines at 0.5, 2, and 10 ppm levels of glyphosate-based formulations whereas regulatory levels of up to 20 ppm in foods (Health Canada. Maximum Residue Limits for Pesticides, 2017) are permitted. Richard et al. (2005) reported disrupts aromatase activity and mRNA levels effect on human placental cell due to glyphosate and roundup and found that it interacts with the active site of the purified enzyme. Matteo et al. (2022) reported occurrence of glyphosate residues between 57 and 983 ng/g in faeces, urine and saliva in forty-two samples of a cattle farm and contrast, 55% of urine and one sample of saliva tested positive. Castilhos Ghisi et al (2021) reported glyphosate toxicity to bees. Ekrem (2021) reported effects of parental synergistic exposure to glyphosate and temperature increase on the next generation in a zebrafish model at low concentration of 1 ppm and 5 ppm for 96 h. Lower survival rate, delay in hatching, increased body malformations and lower blood flow and heart rate were detected in the offspring. In addition, according to the results of whole mouth larva staining, increased apoptosis, free oxygen radical formation and lipid accumulation were detected in the offspring.

Glyphosate also seems to exert a significant toxic effect on neuro transmission, with the glutamatergic system being one of the most affected systems. Glyphosate was found to increase glutamate release and decreased its reuptake, in addition to activating NMDAR and L-VDCC, thus increasing the influx of Ca^{2+} into neurons. Likewise, the results reported reflect the capacity of glyphosate to induce oxidative stress, neuro inflammation, and mitochondrial dysfunction, processes that lead to neuronal death by autophagia, necrosis, or apoptosis, as well as the appearance of behavioral and motor disorders. Although there are important discrepancies between the findings reported in this review, it is unequivocal that exposure to glyphosate, alone or in commercial formulations, can produce important alterations in the structure and function of the nervous system of humans, rodents, fish, and invertebrate animals.

The main toxic effects of glyphosate on mammals based on *in vivo* studies is reported to be endocrine and reproductive disorders (Manservisi et al. (2019), hepatotoxicity, oxidative stress (Benedetti et al.2004), and neurotoxicity (Coullery et al. 2020). The foremost endocrine disturbances observed were alterations in testosterone level, increased 17β-estradiol levels in males serum, reduced spermatogenesis, delayed sexual maturation in females, and alterations in pituitary hormone levels (Owagboriaye et al. 2017). Manservisi et al. (2019) reported endocrine disorders and altered reproductive development in male and female rats due to the effects of exposure to low glyphosate doses in Sprague Dawley rats across different life stage which was administrated 1.75 mg/kg bw/day dose in drinking water from the prenatal period to adulthood. Séralini et al. (2012) reported adverse effect of glyphosate at concentrations well below safety limits on rats which were fed with glyphosate resistant GM maize grains (NK603) which is cultivated world wide (ISAAA 2017). Increased mortality due to development of breast tumors and adverse effect on the pituitary gland, the liver, the digestive tract, and kidneys was reported in females in compared to controls and concluded that low levels of glyphosate induced severe hormone-dependent mammary, hepatic, and kidney disturbances (Séralini et al. 2012). Kubsad et al. (2019) reported negligible effects on the directly exposed F0 or F1 (offspring) female rats generations, however, negative impact in the F2 generation (grand-offspring) and in F3 transgenerational great-grand-offspring were reported that included prostate disease, obesity, kidney disease, ovarian disease, parturition abnormalities, and differential DNA methylation in sperm. El-Shenawy (2009) reported the cytotoxic potential of glyphosate and Roundup in Male albino rats' treated with sublethal concentrations of glyphosate and roundup. Mesnage and Antoniou (2017) reported Proteome disturbances associated with organonitrogen metabolism and fatty acid β-oxidation lipotoxic conditions and oxidative stress based on a combined analysis of the proteome and metabolome profiles of rat livers following long-term (2 years) exposure to an environmentally relevant Roundup dose. The shikimate pathway is absent in animal cells but exists in some microorganisms (Knaggs 2001). Mesnage et al.(2021) reported that glyphosate or its commercial formulations inhibited the shikimate pathway in rat gut microbiome. Some studies have associated shikimic acid to deleterious health effects, such as cancer development (Maand Ning 2019). Ao et al. (2020) is also reported be associated genotoxicity, cytotoxicity and Neurotoxicity with Roundup adjuvant treatment in human lung A549 cells.

Several studies reported the correlation between herbicides exposure and the development of various types of diseases. Organophosphate exposure has been reported to be associated with various human conditions, such as mood disorders, attention deficit hyperactivity disorder, cancer, kidney damage, and autism, among others (Jayasumana et al. 2014). Furthermore, it has been postulated that herbicides may be the main environmental factor associated with the etiology of neurodegenerative diseases, such as Alzheimer's and Parkinson's disease (Swanson et al. 2014). Ferreira et al. (2022) reported effects of glyphosate on the nervous system of various animal and humans and shown that exposure to glyphosate during the early stages of life can seriously affect normal cell development by deregulating some of the signaling pathways involved in this process, leading to alterations in differentiation, neuronal growth, and myelination. Glyphosate also reported to exert a significant toxic effect on neurotransmission and induce oxidative stress, neuroinflammation and mitochondrial dysfunction, processes that lead to neuronal death due to autophagy, necrosis, or apoptosis, as well as the appearance of behavioral and motor disorders at the lower than the limits set by regulatory agencies. This ability of glyphosate to cross both the placental barrier and the blood brain barrier in humans was also reported that detected glyphosate in the brain and cerebrospinal fluid of individuals who had been exposed to glyphosate (Mose et al. 2008). Cardiotoxicity and mortality (Lanzarin et al. 2019), Endocrine disorders (Davico et al. 2020), hepatotoxicity (Rezende et al. 2021), genotoxicity (Rodrigues et al. 2019) and neurotoxicity (Lanzarin et al. 2019) have been reported as toxic effects of glyphosate in fish. Lanzarin et al. (2019) reported increased mortality and malformations in *Danio rerio*embryos exposed to glyphosate concentrations above 8.5 µg/mg. Riaño et al. (2020) reported that exposure to 325 µg /L glyphosate for a period of one month caused liver histological alterations in tadpole.

Osten and Caamal (2017) reported glyphosate concentrations in groundwater (1.42 µg/L) and urine (0.47 µg/L) samples of subsistence farmers from the Francisco J. Mújica communities of rural workers in Mexico and demonstrated excessive use of glyphosate in these agricultural communities. According to Williams et al. (2016), the prevalence rate and mean glyphosate concentration in human urine significantly increased between 1993 and 2016 from 0.00001 to 0.01 mg/kg/bw/ 226/day. Jayasumana et al. (2014) reported the association between glyphosate use and its unique metal-chelating properties with a chronic kidney disease epidemic in Sri Lanka. Likewise, human clinical reports on the effects of intoxication with glyphosate formulations have described harmful effects on the nervous system, including Parkinsonism (Hozyen 2023). Odds ratios and 95% confidence intervals using multivariable logistic regression were used to assess associations between herbicide exposure and autism spectrum disorder (with or without intellectual disabilities) in offspring, adjusting for confounders. von Ehrenstein et al. (2019) reported risk of autism spectrum disorder was associated with prenatal exposure to glyphosate (odds ratio 1.16,95% confidence interval 1.06 to 1.27). Hepatic injury in human is reported to beby glyphosate-surfactant (Mills et al. 2020).

Potential direct and indirect effects of glyphosate use on human health and the environment have triggered a discussion to ban or restrict glyphosate use (Kudsk and Mathiassen 2020). In Europe in 2015, the International Agency on Research on Cancer of the World Health Organization concluded that the glyphosate was 'probably carcinogenic to humans' (Kudsk and Mathiassen 2020). In subsequent assessments, the European Food Safety Authority and the European Chemical Agency concluded that glyphosate could not be classified as a carcinogen (EFSA 2022) which has now extended to 10 more years (https://www.food-safety.com/articles/9138). Independently, several European countries recently announced future bans or massive restrictions on the use of glyphosate (e.g. Austria, Germany, France) (Leonelli 2023). The EU, at large, is to decided on the renewal of the approval of glyphosat in 2023 (EFSA 2022). The decision to approve an active substance such as glyphosate is taken at the EU level. Decisions on the renewal of the approval of glyphosate in the EU are mainly guided by potential environmental and human health risks (EFSA 2022). However, economic implications are inevitably relevant in any decision to ban a product that is widely used and has important implications for the design of production systems.

(iv) Oxyfluorfen

Oxyfluorfen, a phenoxy phenyl-type herbicide is frequently used to control annual grass and broad leaved weeds in soybeans, rice, vegetables, and peanuts. Oxyfluorfen was first introduced by Dow in 1976. Oxyfluorfen is widely used in paddy fields; however, it contaminates the ecosystem's soil and groundwater (Zhao et al. 2016). As a diphenyl ether herbicide, oxyfluorfen impedes photosynthesis *via* hindering chlorophyll synthesis by inactivating the enzyme responsible for the transformation of protoporphyrinogen IX into protoporphyrin, protoporphyrinogen oxidase. Due to high solubility in water and biodegradation, it could cause a substantial hazard to fish and other aquatic species in aquatic environments is suggested (Carboneras et al. 2020) along with a high risk of bioaccumulation in fish (Powe et al. 2018). High mortality at low doses, with the LC_{50} being 3 mg/L for Nile tilapia, *Oreochromis niloticus*, and 4.3 mg/L for *Gambusia affinis* (Hassanein, 2002), 5.9 mg/L for snails, *Biomphalaria alexandrina*, 5.238 mg/L for Japanese medaka embryos, *Oryzias latipes* (Powe et al.2018) and 11.698 mg/L for African catfish, *Clarias gariepinus* (Abd El-Rahman et al. 2019) is reported. However, the oxyfluorfen level of some branches of the Nile reached 23.6 mg/L, which is harmful to the aquatic environment. Several chronic disorders in aquatic organisms, including DNA damage in *Paramisgurnus dabryanus* (Xia et al. 2016) and skeletal deformities in some species of fish (Powe et al. 2018) is also reported by induced by oxyfluorfen. It also causes alterations in the blood hematological profile, oxidative stress, hormonal disruption, and pathological changes in several tissues (Huang et al. 2022).

In living organisms, the reported primary effects from oxyfluorfen exposure studies are inhibition of protoporphyrinogen oxidase resulting in inhibition of heme biosynthesis, and induction of symptoms liver toxicity and anemia (Stagg et al. 2012). In Egypt, 23.6 mg/L oxyflourfen residues in the River Nile (Ibrahim and Sayed, 2020) were reported. Reibach (1990) reported the bioconcentration of oxyfluorfen in the viscera and whole fish.

In aquatic organisms, oxyfluorfen induced DNA damage in *Paramisgurnus dabryanus* (Xia et al. 2016), genome-level deleterious effects, and stunted skeletal growth in some fish species (Powe et al. 2018). Reduced acetylcholinesterase (AChE) content in the brain of *Oreochromis niloticus* and *Gambusia affinis* and induced expression of hepatic and renal heat shock protein is reported by oxyfluorfen (Hassanein et al. 1999). Inhalation of oxyflourfen may be harmful. Contact may cause burns to skin and eyes. Algae and Lemna were identified as the most sensitive species (EFSA 2010) and it pose a high risk in-field for non-target arthropods. No effects on other arthropods such as spiders, beetles, ladybirds, lacewings or parasitic hymenoptera were indicated.

Oxyfluorfen residues with concentration of 4 mg/kg were detected form sediment in US (Riley et al. 1994) while, up to 0.106 mg/kg of oxyfluorfen residues were found in rice grains in India (Sondhia and Dixit 2010). Oxyfluotfen cause risk to non-targeted aquatic life as it inhibits chlorophyll biosynthesis in plants (Geoffroy et al. 2003). Oxyfluorfen affects the early development of zebrafish by impairing lipid and sugar metabolism in the liver, and induces hepatocyte death by upregulating inflammatory factors (Li et al. 2021). In addition, the potential ecological risk to the mollusk, *Biomphalaria glabrata*, and induced death of micronuclei and heteronuclear cells in blood and 0.0239 mg/kg of oxyfluorfen residues in fresh milk. The potential toxic effects of oxyflourfen such as liver cancer, liver failure and haematological effects are recognized in animal (Vasconcelos et al. 2019). One case of an oxyfluorfen poisoning is reported in literature in young man (Couceiro et al. 2017). Oxyfluorfen produced a chemical burn to the fascia and subcutaneous tissue of the forearm.

The person who has genetic inherited disease; variegate porphyria has high risk to oxyfluorfen exposure due to defect of protoporphyrinogen oxidase enzyme (Poletika 2001). Ghada et al. (2019) exposed healthy fish *Chana gariepinus* to 0, 1/10, 1/8, or 1/5 96-h LC_{50} of oxyfluorfen. 96-h LC_{50} of oxyfluorfen was reported to be 11.7 mg/L. Exposure to sublethal levels of oxyfluorfen induced macrocytic hypochromic anemia, leukopenia, lymphopenia, monocytopenia, and eosinopenia. Also, a concentration-dependent increase in alanine transaminase, alkaline phosphatase, aspartate transaminase, urea, creatinine, catalase, and malondialdehyde was detected following oxyfluorfen exposure together with upregulation of catalase gene. But, significant concentration-dependent reductions in AChE, glutathione transferase, reduced to oxidized glutathione ratio, estradiol, and testosterone activities were recorded. These biochemical alterations were accompanied by pathological perturbations in hepatic, renal, brain, and testicular tissues. Following 10 days of recovery, only the hematological impairments were abolished. Conclusively, the herbicides oxyfluorfen could induce multiple negative impacts on *C. gariepinus* with oxidative stress as a probable underlying mechanism. Additionally, a recovery period of 10 days was not enough to restore these impairments.

Chronic exposure to a sublethal level of oxyfluorfen induced severe anemia and leukopenia in fish is reported (Mansour et al. 2023). The DNA fragmentation of the liver increased by 15% in fish compared to the control. Exposure to oxyfluorfen induced a significant reduction in testosterone and luteinizing hormone levels and a significant increase in follicle stimulating hormone and estradiol. Nephrotoxicity of oxyfluorfen to vertebrates is not clear regardless of its wide use (Ferreira et al. 2022). Huang et al. (2022) reported oxyfluorfen as a potential environmental hazard that can cause severe kidney injury and affect the health of organisms. Human embryonic kidney cells HEK293T cells and zebrafish were tested for nephrotoxicity or kidney damage at 2, 4, 6 µg/mL oxyfluorfen for 24 h in vitro, and zebrafish were exposed to 0.4, 0.8, 1.2 mg/L oxyfluorfen for 72 h *in vivo*. Cell migration, oxidative stress and apoptosis caused nephrotoxicity in embryonic and adult zebrafish. Oxyfluorfen induced the secretion of kidney injury markers, including urea nitrogen (BUN), creatinine (CR), and β-n-acetyl-glucosaminidase (NAG) in zebrafish. Additionally, oxyfluorfen affected the homeostasis of oxidant and antioxidant systems, leading to reactiv eoxygen species (ROS) overload. Oxyfluorfen also damaged the glomerular podocytes and induced apoptosis of proximal tubules, which is harmful to normal body function and the renal filtration system Huang et al. (2022).

(vii) Pendimethalin

Pendimethalin is a dinitroaniline group of herbicide. It is approved in many countries in Europe, America, Africa and Asia for weed management in cereals, corn, and soybean. Pendimethalin controls growth of annual grass by inhibiting microtubule assembly, regulating mitosis and cell division. The U.S Environmental Protection Agency (EPA) has classified pendimethalin as a persistent bioaccumlative toxic agent (Singh and Singh 2020) and classified as class C carcinogen (possible carcinogen in human) (El-Sharkawy et al.2011). Several harmful effects of pendimethalin, such as birth defects, cancer (Hou et al. 2006, Arici et al. 2020) and reproductive dysfunction (Ham et al. 2021), genotoxicity (Ansari et al. 2018), oxidative stress, and inflammation (Arici et al. 2020) have been reported. Additionally inhibition of fish embryo development during the early and larvae stages is reported by impeding neurogenesis and vasculogenesis (Wang et al. 2022). In humans, pendimethalin is classified as a possible carcinogen. Ansari et al. (2018) reported genotoxic and apoptotic potentials of pendimethalin in human and animal test models and demonstrated 35.6-fold greater DNA damage by pendimethalin at concentration of 200 µM-treated human lymphocytes. Rat bone-marrow cells, at the highest dose of 50 mg/kg bw/day of pendimethalin also exhibited 10.5-fold greater DNA damage. Pendimethalin at 200 µM and 50 mg/kg bw/day induces 193.4 and 229% higher reactive oxygen species generation in human lymphocytes and rat bone-marrow cells. Pendimethalin exposure results in the appearance of 72.2 and 35.2% sub-G_1 apoptotic peaks in human lymphocytes and rat bone-marrow cells when treated with 200 µM and 50 mg/kg b w/day of pendimethalin. Rats exposed to pendimethalin also reported to imbalance in antioxidant enzymes and histological pathology.

Pendimethalin is reported to be toxic to fish (EPA 2023). Residues of pendimethalin were detected in water sources of many countries after its application in agricultural crops (Coscollà et al. 2017). Pendimethalin degrades slowly in aerobic soil (Sondhia 2012) and the half-life pendimethalin in the range of 12 to 182 days in crops, water, and soils is reported (Sondhia 2014, Chopraet al. 2015). Lee et al. (2022) reported that pendimethalin induces apoptotic cell death through activating ER stress-mediated mitochondrial dysfunction in human umbilical vein endothelial cells. Leeet al. (2022) reported that pendimethalin is harmful to the mammary gland system of cattle, and affecting milk production and caused toxic effects in the mammary epithelial cells (MAC-T) of cattle and induced excessive ROS production and mitochondrial membrane potential (MMP) loss, and disrupted calcium homeostasis and altered the activation of proteins associated with the endoplasmic reticulum (ER) stress response and modified PI3K and MAPK signaling cascades at 0, 2.5, 5 and 10 μM concentration. Jaswal et al. (2022) suggested that pendimethalin may interfere with milk production in cattle and consequently, the dairy industry. Pendimethalin residues were not detected at harvest in the garlic crop however, 0.004 μg/g pendimethalin residues at a dose of 3.0 kg/ha and below detectable limit (BDL) at 0.75 and 1.5 kg/ha in garlic bulbs collected at harvest were reported by Sharma (2014).

It poses a potential risk because of its lipophilicity and strong soil adsorption properties (Verma and Srivastava 2018). In a U.S. Agricultural Health Study, 93 cases of pancreatic cancer were diagnosed subsequent to completing a questionnaire. It was reported that applicators in the top 50% of lifetime pendimethalin use had a 3-fold higher (95% CI: 1.3–7.2, p trend = 0.01) risk compared with never users. Occupational exposure to pendimethalin increased the risk of rectal, lung and pancreatic cancer threefold (Andreotti et al. 2009) through formation of N-nitroso-compounds, that suggesting it carcinogenic effect of nitrosamines on the pancreas (Andreotti et al. 2009). Inversely, Fritschi et al. (2015) reported no relationship between pendimenthalin exposure and risk of pancreatic cancer. According to two long-term animal experiments carried out by EPA, pendimethalin was found to increase the thyroid adenoma in the rats; and was classified as a possible human carcinogen (Group C). In 2014, the Priorities Advisory Group of International Agency for Research on Cancer (IARC) stated that pendimethalin exposure could raise the risks of developing cancers, including lung, rectal, and pancreatic cancers of the gastrointestinal system, and named pendimethalin as a high priority. However, the 2020–2024 Advisory Group report also mentioned that pendimethalin increases oxidative stress biomarkers and suppresses the antioxidant system, and indicated, according to previous research data, the role of oxidative stress in the genetic damages observed after pendimethalin exposure (IARC 2014, 2019). Ham et al.(2021) elucidated the adverse effects of pendimethalin on the reproductive system using mouse testicular Leydig and Sertoli cells (TM3 and TM4 cells, respectively) and confirmed that activation of ER stress and autophagy were blocked by 2-aminoethoxydiphenyl borate (2-APB) treatment and pendimethalin induced cell cycle arrest and apoptosis in TM3 and TM4 cells.

It is generally expected that the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) has been adopted for industrial chemicals in workplace by a significant number of countries, however many of them still follow the FAO Guidelines on Pesticide Registration and the FAO Guidelines on Good Labelling Practice for Pesticides (rather than GHS) to carry out herbicide hazard classification and prepare herbicide labels. Based on GHS, pendimethalin is characterized as category 2, H361d means suspected risk of damaging the unborn child (Warning Reproductive toxicity), H400: Very toxic to aquatic life (Warning Hazardous to the aquatic environment, acute hazard) and H410: Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard] along with Precautionary Statement Codes by GHS as P203, P273, P280, P318, 391, P405, and P501.

(viii) Sulfosulfuron

Sulfosulfuron is a selective, systemic sulfonyl urea herbicide, absorbed through both roots and leaves. It translocates throughout the plant and acts as an inhibitor of amino acid biosynthesis, hence stopping cell division and plant growth. Sulfosulfuron is effective against grasses and broad-leaved weeds in wheat, however barley and oats are sensitive towards sulfosulfuron. Sulfosulfuron is also used for the effective control of *Phalaris minor* in wheat crop (Mohammad 2019). Sulfosulfuron at very low doses, inhibit synthesis of essential amino acid such as leucine, isoleucine, and valine in the sensitive plants. Many studies demonstrated that residue of sulfosulfuron in a soil with high pH, low moisture and organic matter level, and with the short time between herbicide application and the emergence of the following crop. Damage to barley, lens, sorghum, and sunflower as sensitive crop after one year (Moyer and Hamman 2001) is reported by sulfosulfuron residue in Iran at 26.6 g/ha dose. The sulfosulfuron residue significantly reduced cotton plant height and dry matter in the field at the first time of sampling (30 days after emergence) with a reported half-life of 42 days for sulfosulfuron. Adverse effects from sulfosulfuron caused a significant reduction in barley. The most residual injuries were observed in canola in which all traits were reduced by residues of sulfosulfuron used for wheat.

Earthworms are extremely assailable to the adverse effects of these chemicals (Nurhidayati et al. 2012). Sulfosulfuron was found to be more toxic than deltamethrin through contact filter paper test with LC% 0 value of 0.5 µl/ cm^2. Leaching of sulfosulfuron can be reduced by cereal straw and fresh cow dung slurry but cereal straw was more found to be effective, probably because its addition decreases soil pH, thereby causing faster hydrolysis of the herbicide. At harvest time, residues of the herbicide in grains, straw and soil were below recommended maximum residue limits (0.1 mg/kg) with both amendments (Joshi et al. 2019).

In agricultural soils and wetland sediments, sulfosulfuron residues were detected at concentrations of 1.2 to 10 µg/kg (Degenhardt et al. 2010), and depict toxic levels for organisms. A study extending from 2009 to 2011 in the Saint-François Bay, adjacent to the Saint Lawrence River, showed that among 70 water samples, the detection frequencies (>10 ng/L) of sulfosulfuron reached to 7.1 %, respectively with maximum concentrations of 148 and 223 ng/L and this concentration is found to be above the baseline level (100 ng/L) for aquatic plant toxicity and pose potential toxic rise to flora in the streams (de Lafontaine et al. 2014). Kazemi (2022) reported 1.41 and 0.52 µg/kg sulfosulfuron residues at 26.6 g/ha application ae in wheat crop and was found up to 90 and 125 days with half-life of 19 days.

11. Herbicide phytotoxicity and effects on non-target organisms

One of the most critical effect and risks associated with the application of persistent herbicides is the toxicity on sensitive plant species in crop rotations. Herbicides with moderate to persistently high levels in the environment can impose toxic effects on sensitive plants. The effects of different herbicides on non-target plants are presented in Table 16. Application of the sulfosulfuron inhibited the growth of seeded sunflower (Alonso-Prados et al. 2002), even nine months later and caused 40 % of reduction in yield to winter rape seeded in crop rotation (Adamczewski and Paradowski 2004). Wang et al. (2018) found that the residues of same as an HPPD-inhibiting herbicide at the rate of 180 g/ha had a profound phytotoxicity effect on sunflower, coriander, carrot, and radish. Different plant species exhibit different sensitivity or tolerance levels to a specific herbicide concerning biological and morphological characteristics **(Table 16)**.

Table 16. Effects of different herbicides on non-target plants

Herbicide	Mode of action	Group	Non-target plant species	Concentration needs to significant damage	Reference
Glyphosate	EPSPS	9/G	*Lupinus albicaulis*	1002 g/ha	Olszyk et al. 2013
Atrazine	PSII A	5/C	*Pennisetum americanum*	10 mg/kg	Jiang et al. 2016
Sulfosulfuron	ALS	2/B	*Brassica napus*	2.1 µg /kg	Mehdizadeh et al. 2017
2,4-D	SA	4/O	*Phaseolus vulgaris*	0.3 ppm	Cenkci et al. 2010
Pendimethalin	Root/shoot Growth inhibitor	3/K	*Oryza sativa*	1600 g/ha	Ahmed et al. 2015
Oxyfluorfen	PPO	14/E	*Hydrangea paniculata*	0.02 mg /L	Poudyalet al. 2020

Hadizadeh (2021) reported persistence behavior of sulfosulfuron in soil under wheat cropping conditions at 26.6 g/ha and 33.73 g/ ha and reported half-time 33.8 to 25 days with 90% reduction in initial herbicide concentration were from 112.2 and 83.2 days. Saini (2010) reported residual toxicity of sulfosulfuron on maize, bajra, sorghum and bottle gourd, whereas no residual toxicity of these two herbicides was observed in cotton, summer moong, bhindi, dhaincha and muskmelon. Ramesh Atmakuru (2007) reported long term stability of sulfosulfuron in subsoil under the natural wheat cropping conditions by application of sulfosulfuron on soil at 50 g/ha and 100 g/ha. The residues detected were in the range 0.001 to 0.017 µg/g. Toxic classification showed sulfosulfuron H400: Very toxic to aquatic life (Warning Hazardous to the aquatic environment, acute hazard) H410: Very toxic to aquatic life with long lasting effects (Warning Hazardous to the aquatic environment, long-term hazard]. Restricted-entry interval (REI) of 12 hours. Personal protective equipment (PPE) required for early entry to treated areas that is permitted under the Worker Protection Standard and that involves contact with anything that has been treated, such as plants, soil (https://pubchem.ncbi.nlm.nih.gov/compound/Sulfosulfuron#section=Safety-and-Hazards). GHS Hazard Statements for sulfosulfuron are H400: Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard]; H410: Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard] with recautionary Statement Codes; P273, P391, and P501 Hazardous to the aquatic environment (acute) - category 1.

12. Safety measures

Spray of herbicide is a specific work therefore all farmers especially who involved in herbicide spray must be trained on herbicide application based on recommended doses, safe use, disposal and toxicity of herbicides in different crops. Non-selective herbicides must by sprayed by pest control operator (PCO) as notified in the case of glyphosate. Pendimethalin toxicity, occupational exposure to pendimethalin and pendimethalin exposure-related diseases specifically remain insufficiently investigated. On biodiversity, the risks associated with the representative uses of glyphosate are complex and depend on multiple factors. It has been noted that glyphosate commercial formulation products are more toxic than the active ingredient and hence pose a significant risk to human and environment. In view of increasing environmental load, adverse effect on human and animal along with suicidal attempt cases by intake of herbicides viz., 2, 4-D, butachlor, glyphosate, pendimethalin and oxyflourfen are also increasing in India and other countries. Hence excess amount of herbicides should not be stored in house/farms to avoid any negative medical complication associated with misuse of herbicides and they must be sold from authorized dealers. A herbicides dealer should also be educated on safe uses of herbicides and a legal license should be made mandatory for all herbicides to sale. Training and demonstration on use, safety precaution, storage and disposal of herbicides should be given to the farmers' and labours engaged in the herbicide spray work. Dealer should also be educated on immediate mitigation measure or first aid treatment in case of medical emergencies caused by the herbicides.

13. Conclusion

The information provided in the bulletin demonstrated below detection levels or below maximum residue levels of herbicides in agricultural commodities after field application in crops in most of the cases, however, in many cases residue were detected. Herbicide active substances degrade into degradation products which are many time as toxic as the parent molecule and occasionally even more persistent in the environment. Therefore it is not the herbicide use only that is important, it is equivalent important that after application how much is degraded in the soil, plants and how much is reaching to the water bodies and affecting aquatic and other non-targeted organisms at various concentration levels. In India and the world, increasing cases of detection of residues in water, other environment segments and non-target organisms predict a long term risk to human and animals. Therefore, over reliance on herbicides applications for weed management need to be optimized, restricted and regulated in order to prevent environment, human and other organisms from any short term or long term harmful effects. Integrated weed management practices with more consideration to the environmental friendly weed control practice that involved use of bio-herbicides or other alternative methods/techniques should also be promoted in weed management practices. It is suggested to register/renew or restrict/ ban the use of herbicides based on all recently worldwide published scientific studies that give more insight along with earlier scientific data must be taken into consideration.

Residue and toxicological data from other countries should also be considered to reevaluate proposed restriction/ban as well as other herbicides which are banned or restricted in other countries to avoid any long term impacts in India. Acceptable daily intake (ADI) values along with LD_{50} value must be taken in to consideration before recommending a herbicide. If herbicide residues are detected above ADI values, then suspected health risk through consumption of those agricultural product cannot be overruled. Many herbicide formulation products are more toxic then the technical grade, for example glyphosate, hence bioefficacy and toxicity data of inert ingredient should also be considered and must be submitted along with registration of herbicides to safeguard environment and human health and assess any long term impact. Several companies which are registered in India under *me too* registration clause 9 u/s 9(4) FIM/TI/FI (Me Too) are not disclosing inert angriest composition and selling products in the market (for example, Roundup Gold, glyphosate 36%; inert ingredient 62.8%), hence it should also be regulated. Farmers and dealers must be trained on proper use, storage and safe disposal of herbicides as well as they should be made aware on toxic effect of herbicides.

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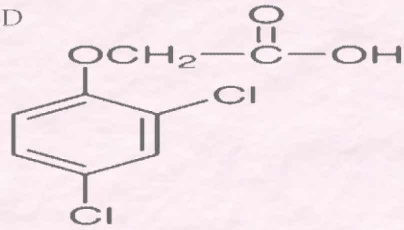
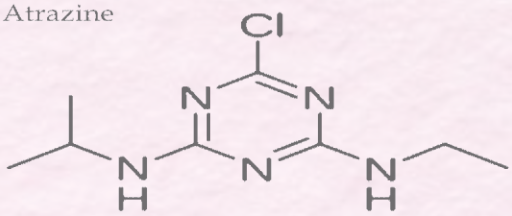
2,4-D



Atrazine



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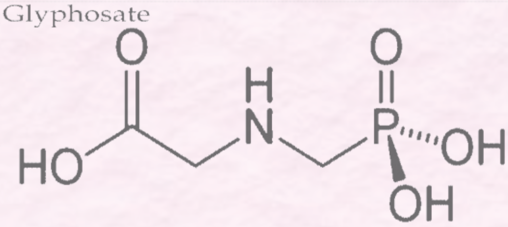

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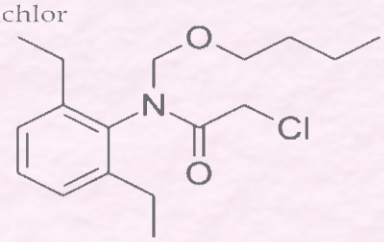

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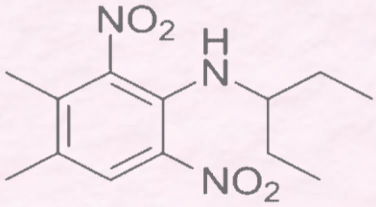

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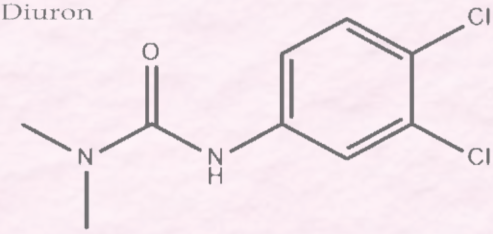

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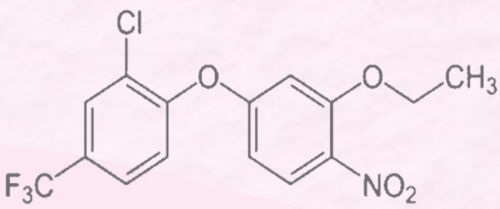

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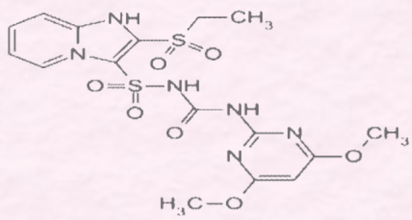

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