# The Mutagenic Effects of Pesticides on Enteric Bacterial Pathogens: A Scoping Review

By

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A thesis submitted to the Department of Mathematics and Natural Sciences in partial fulfillment of the requirements for the degree of Bachelor of Science in Microbiology

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July 2022

## Declaration

It is hereby declared that

1. The thesis submitted is my original work while completing the degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where it is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or any other institution.
4. I have acknowledged all main sources for help.

**Student's Full Name & Signature:**

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## Approval

The thesis/project titled “The Mutagenic Effects of Pesticides on Enteric Bacterial Pathogens: A Scoping Review” submitted by Ashna Ambrin Hoque (18126061) of Spring 2018, has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Science in Microbiology on 19th July, 2022.

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## Abstract

**Background:** Pesticides are chemical substances that are being extensively used worldwide leading to the contamination of environment, particularly in soil and aquatic systems. Thus, enteric bacterial pathogens living in those environments are constantly being exposed to these pesticides. Therefore, the purpose of this scoping review was to assess the potential role of pesticides as mutagens on these bacterial species. Another aspect of this review was to assess the correlation between pesticides and antibiotic resistance as antibiotics are frequently found in the environment along with pesticides.

**Methods:** We used two primary databases (PubMed and Scopus) and one search engine (Google scholar) to search for original articles which highlighted the mutagenic responses of enteric pathogenic bacteria exposed to pesticides. In this review, grey literature was also included from websites (Food and Drug Administration). The data found from the studies were then extracted in a summary table which focused on highlighting the effects pesticides had on different pathogens.

**Results:** Following the inclusion and exclusion criteria, 5889 articles were retrieved after duplications were removed and 85 articles were finally included in the review which tested for 38 insecticides, 25 herbicides and 14 fungicides. Overall, most of the studies focused on Ames test and found that dichlorvos, triclorfon, captan, folpet, diallate, triallate were able to induce base pair substitution and frame-shift mutations. Moreover, a positive correlation between pesticides and antibiotic resistance was also seen though there were only a few studies testing this effect. One study also performed a genome wide mutagenicity testing with glyphosate but found no significant effect on bacteria.

**Conclusion:** Our findings imply that pesticides might be responsible for mutations in enteric pathogens. However, it is difficult to come to a definitive conclusion in case of wild type strains as the publications using Ames test utilized modified strains of the bacteria. It is necessary to study the mutagenic effects of pesticides with wild type strains, and also it is important that more studies of the relation between pesticides and antibiotic resistance are performed so that this may contribute in evaluating the risk assessment of pesticides.

**Keywords:** Pesticides, Mutation, Antibiotic Resistance, Enteric Pathogenic Bacteria, Scoping review

## Acknowledgement

I would like to express my earnest gratitude to the Almighty for enabling me to complete the report in proper health till the end. I am thankful to the Chairperson of the Department of Mathematics and Natural Sciences Professor A M F Yusuf Haider for providing me with the opportunity to complete my undergraduate thesis. I am also grateful to my supervisor, Mahbubul Hasan Siddiqee for his continued support and patients and for guiding me throughout this entire process on writing the thesis. I would also like to thank all of the faculty members who have helped me grow over the years. Finally, I am grateful to my family for their constant love and support which helped me to stay motivated during this process. This journey would not have been a success without their contribution.

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## List of Acronyms

FDA: Food and Drug Administration

FY: Fiscal Year

HGT: Horizontal Gene Transfer

ARG: Antibiotic Resistance Gene

WGS: Whole Genome Sequencing

RND: Resistance Nodulation Division

*E. coli*: *Escherichia coli*

*S. typhi*: *Salmonella typhi*

ROS: Reactive Oxygen Species

MMR: Mismatch Repair

# Chapter 1

## Introduction

Pesticides are chemical substances applied to kill unwanted weeds, insects, rodents, fungi that may damage or destroy crops. These pesticides can be classified based on the pest it targets such as insecticides, fungicides, herbicides, rodenticides etc. Ideally, the pesticide should only eliminate the organism it is meant to target. However, in several occurrences, these chemicals were found to affect non-target organisms, such as humans (Nicolopoulou-Stamati et al., 2016), soil microbes (Mehjin A M AL-Ani et al., 2019), honeybees (Chmiel et al., 2020) and hamper the environment and ecological system. In recent years, the use of pesticides for pest management has increased at an alarming rate, with the amount of worldwide pesticide usage being around 2 million tons, of which about 50% are herbicides, 30% are insecticides, 18% are fungicides and 6% are the remaining pesticides (Sharma et al., 2019).

After the application of pesticides, these substances can pollute the environment through spray drift, runoff, leaching, volatilization. By these mechanisms, they can travel from their application site to soil and water bodies, creating residues and persisting in the environment for a long time depending on their half-life (Akter et al., 2009). Enteric pathogenic bacteria such as *Escherichia coli*, *Salmonella*, *Shigella*, *Campylobacter* etc. are known to enter soil and aquatic ecosystems contaminating the environment (Santamaría & Toranzos, 2003; Pandey et al., 2014). As a result, these bacteria can get exposed to pesticides and their residues and long-term exposure to these organic chemicals can lead to mutations which may encourage the evolution of pathogens.

Antibiotic resistance is also a major factor in contributing to pathogen evolution. Antibiotics can reach the environment by several sources, for example, from manure and sludge that are applied on land for agricultural purpose, and also from urine, manure, feces of human and animals (Du & Liu, 2011). According to literature, approximately 40-90% of administered doses of antibiotic is excreted into the environment through urine and feces (Polianciuc et al., 2020). Constant exposure to antibiotics induces antibiotic resistance in bacteria. Moreover, environmental pollutants can also act as triggers to induce resistance to multiple antibiotics (Buelow et al., 2021). These reports suggest that antibiotics and pesticides can be present together in the environment which might lead

to induction of cross-resistance. Therefore, understanding the ability of pesticides to induce mutation and antibiotic resistance in pathogenic bacteria is crucial in respect to public health.

Until now, studies have mainly focused on reporting the toxicological effects of pesticides (Lushchak et al., 2018; Delorenzo et al., 2009). However, the mutagenic effects of pesticide on bacteria have not been systematically reviewed previously. Therefore, there remains a knowledge gap regarding the true potential of the mutagenic action of pesticides. The objective of this study was to conduct a scoping review of the literature focusing on the mutagenic responses of enteric pathogenic bacteria exposed to pesticides. The findings of this study indicate a possible role of pesticides in causing mutation in bacteria and it also emphasizes the necessity to conduct future studies investigating the connection between pesticide and its mutagenic properties in relation to bacteria.

# Chapter 2

# Methodology

Preferred method of reporting items for systematic Review and meta-Analyses extension for scoping reviews (PRISMA-ScR) was followed for conducting this scoping review (Tricco et al., 2018).

## 2.1 Search Strategy and Data Source

Two databases, Scopus and PubMed were used as the primary data source for this study. Google scholar was also used as a search engine to explore original articles related to the mutagenic effects of pesticides on enteric pathogenic bacteria. The search was done independently by one person from October 2021 to March 2022. Keyterms related to our topic of interest were used to search for articles. These relevant keyterms included bacteria, pathogen, pathogenic bacteria, enteric bacteria, mutation, mutagenesis, mutagenicity, point mutation, frameshift mutation, mutagenic effect, drug resistance, antibiotic resistance. When searching, these search terms were combined with individual name of pesticides. Reference list of individual articles were also explored to ensure that search efficiency was maximized.

## 2.2 Eligibility Criteria

The scoping review was performed to find out studies that reported mutagenic effects caused by pesticides. The inclusion criteria included were – 1) Articles that highlighted effects on enteric pathogenic bacteria, 2) Studies highlighting pesticides and their metabolites, 3) Studies involving effects of pesticide mixtures and also those that highlighted combination of pesticides with other chemicals, 4) Original peer reviewed papers, 5) Studies that were conducted in English. In order to have the inclusion as broad as possible, there were no restrictions on the date of publication and study design. Thus, relevant papers were found from the year 1972 to 2021. Finally, to search for the individual names of pesticides – Food and Drug administration pesticide residue monitoring program report of Fiscal Year 2019 was utilized (Pesticide Residue Monitoring Report and Data for FY 2019, FDA 2021).

The exclusion criteria that were applied included – 1) Studies involving effects tested on organisms other than enteric pathogenic bacteria, 2) Articles highlighting other effects than mutation such as

toxicological effects, 3) Studies that did not specify which pesticide caused the mutation, 4) Review articles, 5) Non peer reviewed articles, 6) Letters or editors, 7) Studies conducted in languages other than English, 8) Studies that met inclusion criteria but full text could not be found.

Microsoft word was used to prepare Graphs and Tables (Result section). Mendeley Desktop software (version 1.19.8) was used to manage references and remove duplicates. After removing duplicates, titles and abstracts were screened after which full text screening was implemented for the relevant articles. Studies were excluded if the inclusion criteria were not fulfilled.

### 2.3 Data Extraction

A summary table was used so that the data found from the selected studies could be extracted. For each study, the table contained the following sections: Title of publication, name of first author, date of publication, Country, Pesticide assessed, Bacteria used, method used to detect mutational effects, key findings. To ensure that the data extracted were accurate, the included articles were revisited multiple times. These data were used to obtain our desired results.

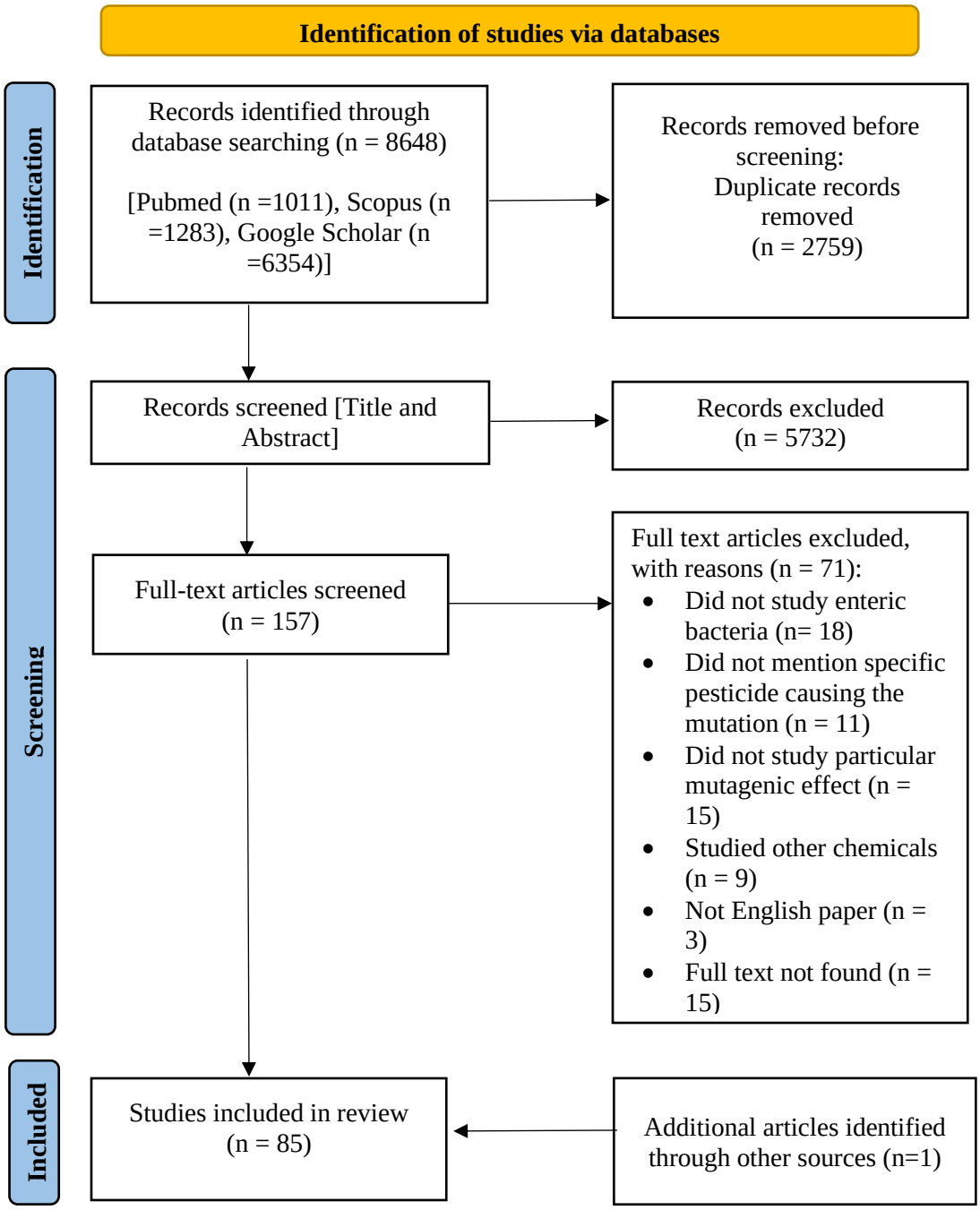


**Figure:** Process of searching and selecting articles included in the scoping review based on the PRISMA 2020 flow diagram

**Table 1: Characteristics of the selected studies**

| References | Publication Year | Country | Pesticide Assessed | Organism Used | Method Used | Major findings |
|---|---|---|---|---|---|---|
| 1. Herbicide promotes the conjugative transfer of multi-resistance genes by facilitating cellular contact and plasmid transfer<br><br>Li, X. et al. | 2021 | China | Glyphosate, Glufosinate and Dicamba | *Donor: Escherichia coli strain* HB101 (E. *coli* HB101)<br><br>Recipient: *E. coli* DH5 α strain | The donor and recipient strains were cultured in medium containing the particular herbicides | The herbicides could increase the conjugative transfer of ARGs between the recipient and donor by inducing mechanisms such as compact cell-to-cell contact by enhancing pilus-encoded gene expression and decreasing cell surface charge, increasing cell membrane permeability, and enhancing the proton motive force, providing additional power for DNA uptake |
| 2. Prochloraz alone or in combination with nano-CuO promotes the conjugative transfer of antibiotic resistance genes between Escherichia coli in pure water<br><br>Guo, A. et al. | 2021 | China | Prochloraz | *Donor:* The *E. coli* DH5α,<br><br>Recipient: The *E. coli* HB101 | The donor and recipient strains were cultured in medium containing prochloraz in presence or absence of nano-CuO | Though prochloraz itself could increase conjugative transfer of ARGs, prochloraz with nano-CuO was able to increase gene transfer more significantly |

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| 3. Genotoxicity of dicrotophos, an organophosphorous pesticide, assessed with different assays in vitro<br><br>Wu J. C. | 2010 | China | Dicrotophos | Salmonella typhimurium strains TA 97a, TA98, TA100, TA102, and TA1535 | Ames test | Only mutagenic towards S. typhimurium TA 97a, TA98, TA100, TA102, and TA1535 at the highest concentration (5000 lg/plate) irrespective of metabolic activation. |
| 4. Assessment of cytotoxicity and mutagenicity of insecticide Demond EC25 in Allium cepa and Ames Test<br><br>A. Özkara | 2019 | Turkey | Demond EC 25 (Deltamethrin) | S. typhi TA98 and TA100 | Ames test | Demond EC25 was found to be mutagenic in 800 and 400 µg/plate doses of TA98 without S9 mix and in 800 µg/plate with S9 mix. In TA100, Demond EC25 was found to be mutagenic only 800 µg/plate doses without S9 mix. |
| 5. Testing of the mutagenicity and genotoxicity of metolcarb by using both Ames-Salmonella and Allium test<br><br>Liman, R. et al. | 2010 | Turkey | Metolcarb | S. typhi TA97, TA98, TA100 and TA102 | Ames test | 0.1, 1 and 10 lg/ plate doses of metolcarb were found to be mutagenic S. typhimurium TA98 without S9. Revertant colony numbers in TA97, TA100 and TA102 became stronger when S9 was added. |
| 6. Investigation of mutagenic | 2010 | Turkey | 2,4-D, 4-CPA | *Salmonella typhimurium* | Ames test | No effect in presence or absence of S9 |

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| effects of some plant growth regulators on Salmonella - microsome test system<br><br>Uysal, A. et al. | | | | strains TA 98 and TA 100 | | |
| 7. Mutagenicity of trifluralin in salmonella-microsome assay under various metabolic activation conditions<br><br>Diril, N. & Sümer, S. | 2008 | Turkey | Trifularin | S. typhi TA98 and TA100 | Ames test | Trifularin was weakly mutagenic in TA98 in presence of S9, no mutagenic activity in absence of S9 |
| 8. Cytogenetic and genotoxic effects of the insecticides, imidacloprid and methamidophos<br><br>Karabay, N. U & Oguz, M. G | 2005 | Turkey | Imidacloprid, Methamidophos | TA100, TA98 of *S. typhimurium* | Ames test | Dose-related increases in the number of revertants were observed with the two *Salmonella* strains (TA98 and TA100). All tested doses of the insecticides demonstrated mutagenic activity in the presence of S9 mix |
| 9. Effects of sub-lethal concentrations of copper ammonium acetate, pyrethrins | 2019 | New Zealand | Atranex WG (Atrazine) | E. coli | Bacteria were cultured in LB medium containing antibiotic and herbicide | Atrazine was able to induce slight antibiotic resistance with ciprofloxacin, streptomycin and kanamycin |

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| and atrazine on the response of Escherichia coli to antibiotics<br><br>Jun, H. et al. | | | | | | |
| 10. Agrichemicals and antibiotics in combination increase antibiotic resistance evolution<br><br>Kurenbach, B. et al. | 2018 | New Zealand | Roundup, Kamba, 2,4-D | E. coli and S. typhi | Bacteria were cultured in LB medium containing antibiotic and herbicide | Roundup, Kamba, 2,4-D were able to increase MIC of Antibiotics |
| 11. Herbicide ingredients change Salmonella enterica sv. Typhimurium and Escherichia coli antibiotic responses<br><br>Kurenbach, B. et al. | 2017 | New Zealand | Glyphosate, Dicamba, 2,4-D | S. typhi enterica and E. coli | Bacteria were cultured in LB medium containing antibiotic and herbicide | Each herbicide could induce increase or decrease in resistance to antibiotics depending on the antibiotic, herbicide, species tested with |
| 12. Sublethal Exposure to Commercial Formulations of the Herbicides Dicamba, 2,4-Dichlorophenoxyacetic Acid and Glyphosate Cause | 2015 | New Zealand | Roundup, Kamba, 2,4-D | S. typhi enterica and E. coli | Bacteria were cultured in LB medium containing antibiotic and herbicide | Each herbicide could induce increase or decrease in resistance to antibiotics depending on the antibiotic, herbicide, species tested with |

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| Changes in Antibiotic Susceptibility in E. coli and S. enterica<br><br>Kurenbach, B. et al. | | | | | | |
| 13. Limitations of pesticide genotoxicity testing using the bacterial in vitro method<br><br>Ilyushina, N. et al. | 2019 | Russia | 2,4-D, Acetamiprid, Azoxystrobin, Chlorothalonil, Clopyralid, Cypermethrin, Cyproconazole, Dicamba, Difenoconazole, Dimethoate, Dimethomorph, Diquat, Fipronil, Flutriafol, Glyphosate, Imazalil, Imazethapyr, Imidacloprid, Pendimethalin, Phenmedipham, Picloram, Prometryn, Propiconazole, Pirimiphos-methyl, Tebuconazole, Thiabendazole, Thiacloprid | Salmonella typhimurium strains TA97, TA98, TA1535. TA100 and TA102 | Ames test | Pirimiphos-methyl increased revertant colonies in TA1535. Pendimethalin and Dimethoate reverted colonies in all strains. Azoxystrobin only reverted colonies in TA98 in absence of S9 metabolic system. |
| 14. The Glyphosate-Based Herbicide Roundup Does Not Elevate Genome-Wide Mutagenesis of Escherichia coli | 2017 | USA | Glyphosate (Roundup) | Wild-type K-12 MG1655 strain and DmutS strain lacking DNA mismatch repair | Whole genome sequencing | Mutation rate of base pair substitution, enhancing a specific gene, transposable elements, deletion of prophage, chromosomal duplication were analyzed by applying glyphosate but |

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| Tincher, C. et al. | | | | | | no effect was seen. |
| 15. Effect of butylated hydroxytoluene and butylated hydroxyanisole on the mutagenicity of 3,2'-dimethyl-4-aminobiphenyl<br><br>Reddy, B. S. et al. | 2009 | USA | Butylated hydroxyanisole (BHA) | S. typhi TA100, TA98 | Ames test | BHA showed antagonistic effect by inhibiting mutagenicity of 3,2´-dimethyl-4-aminobiphenyl (DMAB) |
| 16. Mutagenicity of N-nitroso derivatives of carbofuran and its toxic metabolites<br><br>Nelson, J. et al. | 2009 | USA | Carbofuran, its metabolites 3-hydroxycarbofuran, and 3-ketocarbofuran and their nitroso derivatives | S. typhi TA98 and TA100 | Ames test | Nitroso derivative compounds were mutagenic in TA100 without S9 mix rather than in S9 mix, No mutagenicity in TA98 strain and parent compounds were not mutagenic in any strain in presence or absence of S9 |
| 17. Ames assays and unscheduled DNA synthesis assays on chlorophenoxyacetic acid and its derivatives.<br><br>Charles, J. M. et al. | 1999 | USA | 2,4-Dichlorophenoxyacetic acid and its derivatives | S. typhi TA98, TA100, TA1535 TA1537, TA1538 | Ames test | No effect in presence or absence of S9 |
| 18. Mutagenic interactions of model | 1998 | USA | Pentachlorophenol | S. typhi TA97a, TA98, and TA100 | Ames test | Pentachlorophenol was inactive in all |

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| chemical mixtures<br><br>Donnelly, K. C. et al. | | | | | | strains both with and without metabolic activation, Mixture of pentachlorophenol benzo(a)pyrene (B(a)P) or 2,4,6-trinitrotoluene (TNT) also had no effect on the mutagenicity |
| 19. Pentachlorophenol-mediated mutagenic synergy with aromatic amines in Salmonella typhimurium<br><br>Gichner, T. et al. | 1998 | USA | Pentachlorophenol (PCP) | S. typhi TA1538, TA100, YG1024, YG1029, TA98/1,8-DNP6, MP153 | Ames test | PCP displayed a synergistic relationship to 2-acetoxyacetylaminofluorene (2-AAF) and 2-aminofluorene (2-AF) by increasing their mutagenic capability |
| 20. Lack of genotoxicity of piperonyl butoxide<br><br>Butler, W. H. et al. | 1996 | USA/UK | Piperonyl butoxide | S. typhi TA98, TAI00, TA1535, TA1537 and TA1538, | Ames test | No effect in presence or absence of S9 |
| 21. Evaluation of the genetic toxicity of the organophosphate insecticide chlorpyrifos<br><br>Gollapudi, B. B. et al. | 1995 | USA | Chlorpyrifos | S. typhi TA98, TA100, TA1535, TA1537, TA1538 | Ames test | No effect in presence or absence of S9 |

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| 22. Determination of mutational spectrum of the pesticide, captan, with an improved set of Escherichia coli LacZ mutants<br><br>Lu, C. et al. | 1995 | USA | Captan | Escherichia coli strains CL101P, CL102P, CL103P, CL104P, CL105P, and CL106P | LacZ reversion test (version of Ames test) | Captan induced mutagenesis in all the strains mostly by displaying AT base pair transition or transversion mutation |
| 23. Evaluation of carbendazim for gene mutations in the Salmonella-Ames plate-incorporation assay the role of aminophenazine impurities<br><br>Sarrif, A. M. et al. | 1993 | USA | Carbendazim | S. typhi TA98, TA1537, TA100 and TA1535 | Ames test | Purified carbendazim is not mutagenic but carbendazim with levels of 2,3-diaminophenazine (DAP) and 2-amino-3-hydroxyphenazine (AHP) showed mutation in TA98 with S9 and weakly mutagenic to TA1537 |
| 24. Salmonella mutagenicity tests V. Results from the testing of 311 chemicals<br><br>Zeiger, E. et al. | 1992 | USA | Captan, p,p'-DDT, Glyphosate, Technical grate of Chlordane, Coumaphos | S. typhi TA97, TA98, TA100, TA102, TA104, TA1535, TA1537 and TA1538 | Ames test | Captan, chlordane were positive, DDT, Coumaphos , Glyphosate were negative |
| 25. Effects of synthetic antioxidants (BHA, BHT and PG) on the mutagenicit | 1991 | USA | Butylated hydroxyanisole (BHA) | S. typhi TA100, TA98 | Ames test | BHA alone was not mutagenic in presence or absence of S9 fraction, BHA showed antagonistic |

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| y of IQ-like compounds<br><br>Chen, C. et al. | | | | | | effect by inhibiting mutagenicity of IQ, MeIQ and MeIQx in the strains with metabolic activation |
| 26. Genotoxicity studies on the preemergence herbicide trifluralin<br><br>Garriott, M. L. | 1991 | USA | Trifluralin | S. typhi TA98, TA100, TA1535, TA1537, or TA1538 | Ames test | No effect in any strains in both presence and absence of S9 system. |
| 27. Genotoxicity assessment of atrazine and some major metabolites in the Ames test<br><br>Butler M. A. & Hoagland, R. E. | 1989 | USA | Atrazine and its metabolites hydroxyatrazine, and 2-chloro-4-amino-6-{isopropylamino)-s-triazine 2-chloro-4-amino-6-diamino-striazine and 2-chloro-4-amino-6-(ethylamino)-s-Triazine | S. typhi TA97, TA98, TA100 | Ames test | No mutagenic activity. Metabolic system was not used. |
| 28. An evaluation of the genotoxic potential of glyphosate<br><br>Li, A. P. et al. | 1987 | USA | Glyphosate | S. typhi TA100, TA1537, TA1538, and TA98, E.coli WP2 | Ames test | No significant effects in presence or absence of S9 system |
| 29. Assessment of the mutagenicity of fractions from s-triazine-treated Zea mays. | 1987 | USA | Atrazine | S. typhi TA100 | Ames test | Maize plants exposed to atrazine were seen to be mutagenic in S. typhi TA100 strain by reverting the histidine |

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| Means, J. C. et al. | | | | | | auxotroph back to prototroph |
| 30. Reproducibility of microbial mutagenicity assays II. Testing of carcinogens and noncarcinogens in Salmonella typhimurium and Escherichia coli<br><br>Duckel, V. C. et al. | 1985 | USA | Coumaphos, Diazinon | S. typhi TA98, TA100, TA1535, TA1537, and TA1538, E. coli WP2 | Ames test | No effect in S. typhi in presence or absence of S9, No effect in E. coli as well |
| 31. Mutagenicity testing of agent orange components and related chemicals<br><br>Mortelmans, K. et al. | 1984 | USA | 2,4-D, 2,4-D/dimethylamine salt, 2,4-D n-butyl ester, 2,4,5-T, 2,4,5-T n-butyl and isobutyl esters, 2,4-D (isoocytl ester) and 2,4,5-T (isooctyl ester) | Salmonella Typherium Tester strains TA98, Ta100, TA1535, and TA1537. | Ames Test | No effect in presence or absence of S9 |
| 32. An evaluation of the genotoxic properties of herbicides following plant and animal activation<br><br>Plewa, M. J. et al. | 1984 | USA | Commercial and technical grades of Alachlor, Atrazine, Dicamba, Metolachlor | S. typhi strains TA1535, TA1537, TA1538, TA98 and TA100 | Ames test | No mutagenic properties detected for the commercial grade of dicamba and the technical grade of metolachlor The technical grade dicamba was mutagenic without activation in strain TA1535 and following plant activation in |

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| | | | | | | strains TA1538 and TA100. The commercial grade of metolachlor was positive in TA1538 and positive after S9 activation in TA100. Combinations of commercial grade herbicides positive only after plant activation- metolachlor plus atrazine |
| 33. Potential of 2,4-dichlorophenoxyacetic acid conjugates as promutagens in the Salmonella-microsome mutagenicity test<br><br>Rashid, K. A. | 1984 | USA | 2, 4-Dichlorophenoxyacetic acid (Alanine, Aspartic acid, Leucine, Methionine and Tryptophan | S. typhi TA97, TA98, TA100, TA1535, TA1538 | Ames test | No effect in presence or absence of rat and woodchuck S9 preparation. |
| 34. Evaluation of the mutagenic potential of corn (Zea mays L.) grown in untreated and atrazine (AAtrex) treated soil in the field | 1984 | USA | Atrazine | S. typhi TA100 | Ames test | Treated and untreated corn plants with atrazine were equally able to revert the histidine auxotroph back to prototroph |

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| Sumner, D. D. et al. | | | | | | |
| 35. Aliphatic halogenated hydrocarbons produce volatile Salmonella mutagens<br><br>Distlerath, L. M. et al. | 1983 | USA | Diallate, Triallate | S. typhi TA100 | Ames test | In presence of S9, both compounds were mutagenic |
| 36. Mutagenicity assays with (2,4-dichlorophenoxy) acetic acid--amino acid conjugates<br><br>Rashid, K. A. & Mumma, R. O. | 1983 | USA | Five amino acid conjugates of 2,4-D (Alanine, Aspartic acid, Leucine, Methionine, and Tryptophan) | five *Salmonella typhimurium* strains (TA97, TA98, TA100, TA1535, and TA1538 | Ames test | No effect seen for any amino acid conjugate |
| 37. Evaluation of diallate and triallate herbicides for genotoxic effects in a battery of in vitro and short-term in vivo tests<br><br>Sandhu, S. S. et al. | 1983 | USA | Commercial-grade of Diallate and Triallate | Salmonella tester strains TA1535, TA1537, TA1538, TA98, and TA100 | Ames test | TA1535, TA98, and TA100 gave positive responses only with metabolic activation Weaker mutagenic activity of diallate was seen in one experiment without activation in strain TA1535 and TA100. Negative results were seen in TA1537 with or without |

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| | | | | | | metabolic activation |
| 38. Determining pesticide mutagenicity and DNA-damaging activity with Bacillus subtilis and Salmonella typhimurium<br><br>Huff, R. A | 1982 | USA | Ethoxiquin | S. typhi TA1535, TA1537, TA1538, TA98, TA100 | Ames test | No effect |
| 39. An evaluation of the genotoxic properties of insecticides following plant and animal activation<br><br>Gentile, J. M. et al. | 1981 | USA | Commercial and technical grades of Carbofuran, Chlordane, Chlorpyrifos, Heptachlor, Phorate | S. typhi TA1535, TA1537, TA1538, TA98, and TA100 | Ames test | No effect for carbofuran, chlordane, chlorpyrifos, phorate. Technical grade of heptachlor positive after plant activation in TA1535 and animal activation in TA100 |
| 40. Pesticide mutagenicity in Bacillus subtilis and Salmonella typhimurium detectors<br><br>Shiau, S. Y. et al. | 1981 | USA | Captan, Folpet, Triallate | S. typhi TA1535, TA1536, TA1537, TA1538, TA98, and TA100 | Ames test | Captan mutagenic in all strains except TA1536, Folpet only mutagenic in TA100, Triallate mutagenic in TA1535 and TA100. S9 mix decrease mutagenic activity |
| 41. Mutagenicity tests of diflubenzur | 1978 | USA | Technical grade of Diflubenzuron | S. typhi TA100, TA98, | Ames test | No mutagenic effect occurred |

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| on in the micronucleus test in mice, the L5178Y mouse lymphoma forward mutation assay, and the Ames Salmonella reverse mutation test<br><br>Macgregor, J. T. et al. | | | and Dimilin W-25 (wettable powder form of Diflubenzuron) | TA1535 and TA1537 | | in presence or absence of S9 |
| 42. Metabolism of diflubenzuron by soil microorganisms and mutagenicity of the metabolites<br><br>Seuferer, S. L. | 1978 | USA | Metabolites of Diflubenzuron - 2,6-difluorobenzoic acid, 4-chlorophenylurea, 4-chloroaniline, 4-chloroacetanilide, acetanilide, and 4-chlorophenol | S. typhi TA98, TA100, TA1535, TA1537, or TA1538 | Ames test | 2,6 difluorobenzoic acid gave a false positive at high concentrations because of its lethal effect on the test bacterium. The metabolites 4-chloroaniline, 4-chlorophenol, and 4-chlorophenylurea were borderline mutagens. |
| 43. Mutagenicity screening of five methyl carbamate insecticides and their nitroso derivatives using mutants of Salmonella | 1977 | USA | Carbaryl, Methomyl and their nitroso derivatives | S. typhi TA98, his TA100, his TA1535, his TA1537 and his TA1538 | Ames test | Parent compounds were not mutagenic. Nitroso derivatives were strongly mutagenic in TA100 and TA1535 |

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| typhimurium LT2<br><br>Blevins, R. D. et al. | | | | | | |
| 44. Mutagenicity of dieldrin in the Salmonella - microsome test<br><br>Majumdar, S. K. et al. | 1977 | USA | Dieldrin | S. typhi TA98, TA100, TA1535 | Ames test | More mutagenicity after S9 activation in all strains compared to without S9 activation |
| 45. Screening of pesticides for mutagenic potential using Salmonella typhimurium mutants<br><br>Marshall, T. C. et al. | 1976 | USA | Nitrosocarbaryl, Captan, DDT, Heptachlor, Heptachlor epoxide, Dieldrin, Carbaryl, Linuron, and Diazinon | S. typhi TA1535, TA1536, TA1537, and TA1538 | Ames test | Nitrosocarbaryl proved to be a potent base-pair substitution mutagen (TA1535) and a frameshift mutagen (1537 and 1538). Captan showed both frameshift (1537) and base-pair substitution (TA1535) mutagenesis. The mutagenic properties of these two compounds decreased when exposed to rat liver homogenate. The others had no effect |
| 46. Evaluation of herbicides for possible mutagenic properties | 1972 | USA | Atrazine, Bromoxynil, 4-CPA, 2,4-D, DCPA, Diallate, Dicamba, Diuron, Linuron, | Histidine-requiring mutants of Salmonella typhimurium designated as either nonsense | Ames test | None were mutagenic |

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| Andersen, K. J. et al. | | | Picloram, Prometryn, Trifluralin, Triallate, | (amber or ochre), missense, or frameshift mutants | | |
| 47. The herbicides trifluralin and tebuthiuron have no genotoxic or mutagenic potential as evidenced by genetic tests<br><br>Franco-Bernardes, M. F et al. | 2017 | Brazil | Trifluralin and Tebuthiuron | TA97a, TA98, TA100, and TA1535 strains of Salmonella typhimurium | Ames test | The two pesticides were not mutagenic to any strain at any concentrations comparing with the negative and positive control in presence and absence of S9 |
| 48. Determination of mutagenic potential of imidacloprid in Salmonella typhimurium–TA 98 and TA 100 following bacterial reverse mutation assay<br><br>Kumar, A. et al. | 2013 | India | Imidacloprid | TA100, TA98 of S. typhimunum | Ames test | There was observed a dose dependent increase in the number of revertant colonies in both strains of Salmonella typhimurium - TA98 and TA100. No metabolic system used. |
| 49. DNA damage and mutagenicity induced by endosulfan and its metabolites | 2006 | India | Endosulfan and its metabolites | S. typhi TA98, TA97a, TA102, TA104, and TA100 | Ames test | Endosulfan wass mutagenic in TA100 and TA102, the remaining compounds produced consistently strong responses |

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| Bajpayee, M. et al. | | | | | | (>three-fold background) in TA98, with a frame shift mutation in the his D gene, followed by TA97a >TA102 > TA100 > TA104. Diol and hydroxyether metabolites producing the highest responses. S9 slightly enhanced the mutagenicity of endosulfan and three of its metabolites (endosulfan ether, hydroxyether, and lactone) in at least some strains, while having little effect on the mutagenicity of the other compounds. |
| 50. Mutagenic and genotoxic activities of four pesticides captan, foltaf, phosphamidon and furadan<br><br>Saxena, S. et al. | 1997 | India | Captan, Furadan (trade name of Carbofuran) | S. typhi strains TA 97a, TA100, TA104, TA98 and TA102 | Ames test | Captan was more mutagenic to 97a, TA100, TA104 and weakly mutagenic to TA98 and TA102 in the absence of metabolic activation. But mutagenicity decreased with presence of S9. |

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| | | | | | | Furadan induced most revertant colonies in TA104 and then in TA102. Not much revertant colonies were seen in the other strains. |
| 51. Evaluation of the mutagenic potential of endosulfan using the Salmonella - mammalian microsome assay<br><br>Pandey, N. et al. | 1990 | India | Endosulfan | S. typhi TA97(a), TA98, TA100 and TA102 | Ames test | Plate incorporation studies did not show mutagenic response with any of the tester strains used. A modification of the assay using a preincubation procedure showed mutagenic activity with and without metabolic activation with TA97(a) only. Increased toxicity was observed after addition of phenobarbital-induced S9 mix. |
| 52. Assessment of the mutagenic potential of a fungicide Bavistin using multiple assays.<br><br>Pandita, T. K. | 1987 | India | Bavistin (Carbendazim) | S. typhi TA98, TA100 | Ames test | No effect in presence of absence of S9 |

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| 53. Evaluation of mutagenic activities of endosulfan, phosalone, malathion, and permethrin, before and after metabolic activation, in the Ames Salmonella test<br><br>Pednekar, M. D. et al. | 1987 | India | Endosulfan, Phosalone, Malathion and Permethrin | S. typhi TA97(a), TA98, TA100 | Ames test | Endosulfan, phosalone, malathion and permethrin (at non-toxic and 90% toxic doses) showed no mutagenic effects in absence or presence of S9 |
| 54. Differential mutagenic response of Salmonella typhimurium to the plant-metabolized organophosphorus insecticides, phoxim and azinphos methyl<br><br>Arroyo, S. G. et al. | 2007 | Mexico | Phoxim | *S. typhi* tester strains TA98 and TA100 | Ames test | Phoxim mutagenic without metabolic activation in both strains. No mutagenicity with plant activation.<br>At higher concentrations, a decrease in the number of revertants suggested a toxic effect. |
| 55. Analysis of photomutagenicity of thiabendazole with UVA irradiation absence of 8-hydroxyguanosine formation | 2006 | Japan | Thiabendazole (TBZ), Tricyclazole, Imazalil | S. typhi TA100 (hisG46, uvrB, rfa/pKM101), TA98 (hisD3052, uvrB, rfa/pKM101), and E. coli strain WP2uvrA/pKM101 | Ames test | Only UVA-preirradiated TBZ induced reverse mutations in WP2uvrA/pKM101 and TA100. |

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| Akanuma, N. W. et al. | | | | | | |
| 56. Photomutagenicity of thiabendazole, a postharvest fungicide, in bacterial assays<br><br>Akanuma, M. W. et al. | 2003 | Japan | Thiabendazole (TBZ) | *Salmonella typhimurium* strains TA1535, TA1538, TA98, and TA100, and *Escherichia coli* strains WP2, WP2*uvrA*, WP2/pKM101, and WP2*uvrA*/ pKM101 | Lac reversion test same as Ames test | TBZ alone not positive. irradiated TBZ was positive. A strong photomutagenic effect was observed in E. coli WP2uvrA and E. coli WP2uvrA/pKM101. TBZ at the same concentration was weakly photomutagenic in S. typhimurium TA100 and TA98, Not photomutagenic in TA1535, TA1538, WP2. WP2/pKM101 |
| 57. Co-mutagenic activity of phenoxyherbicides MCPA- and MCPB-ethylester in the Ames assay<br><br>Shibuya, N. et al. | 1990 | Japan | MCPA | TA100, TA98 of S. typhimunum | Ames test | No effect on its own but could slightly increase mutagenicity of 2-AA |
| 58. Further mutagenicity studies on pesticides in bacterial reversion | 1982 | Japan | Acephate, Chlorpyrifos, Diazinon, Dichlorvos, Ethion, Dimethoate, Malathion, | S. typhi TA 100, TA98, TA 1535, TA 1537 and TA 1538, (WP2 hcr) of Escherichia coil | Ames test | Acephate, Dichlorvos, Dimethoate, Monocrotophos, Phosmet, Trichlorfon |

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| assay systems<br><br>Moriya, M. et al. | | | Monocrotophos, Phosmet, Phoxim, Trichlorfon, Captan, Chlorothalonil, Folpet, Thiabendazol, Thiophanatemethyl, Glyphosate, 2,4-D, Carbofuran Dicamba, MCPA, Pentachlorophenol, Diuron, Linuron, Alachlor, Trifluralin | | | dithiocarbamates were positive only in the base-change-type strains (WP2 hcr, TA1535 and TA100), Captan, folpet showed mutagenicity for all 6 strains. Carbofuran was positive only in the frameshift-type strains. Phosmet was enhanced by addition of the S9 mix, acephate, dimethoate, monocrotophos, trichlorfon, carbofuran,were not so much affected by the S9 mix |
| 59. Mutagenicity screening of pesticides in the microbial system<br><br>Shirasu, Y. et al. | 1976 | Japan | Captan, Dichlorvos, Folpet | E. coli (B/r try WP2 [24] and WP2 try hcr and S. typhi TA1535, TA1536, TA1537 and TA1538 | Ames test | All three compounds were mutagenic in E. coli and in S. typhi TA1535 strain. |
| 60. Ability of Insecticidal Formulations to Support Growth of Bacteria and the Absence of Their Mutagenic | 2006 | Jordan | Vapcocidine-20 FL (Fenvalerate) and Cypermethrin-10 FL (Cypermethrin) | S. typhi tester strain TA1530, TA1537 | Ames test | No effect |

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| Activity in the Ames Salmonella Test<br><br>Saadoun, I et al. | | | | | | |
| 61. Evaluation of the Genetic Toxicity of Synthetic Chemicals (VII)-A Synthetic Selective Herbicide, Pendimethalin<br><br>Ryu, J. C. & Kim. K. R. | 2003 | Korea | Pendimethalin | S. typhi TA98, TA100, TA1535, TA1537 | Ames test | In presence and absence of S9, pendimethalin showed dose dependent mutagenicity in TA1537 and TA98, and TA100 was affected only in absence of S9, slightly mutagenic in TA1535 in presence of S9. |
| 62. Evaluation of the genetic toxicity of synthetic chemicals (II), a pyrethroid insecticide, fenpropathrin<br><br>Ryu, J. C. et al. | 1996 | Korea | Fenpropathrin | S. typhi TA98, TA100, TA1535, TA1537 | Ames test | No effect in presence or absence of S9 |
| 63. Comparative investigation on the mutagenicities of organophosphate, phthalimide, pyrethroid and carbamate insecticides | 1998 | Taiwan | Acephate, Allethrin, Captan, Carbofuran, Chlorpyrifos, Dichlorvos, Ethion, Folpet, Malathion, Monocrotophos, Permethrin | S. typhi TA100, TA1535, JK3 and JK947, TA98, JK1 | Ames and Beta lactam test | Lactam test: Allethrin, captan, folpet, monocrotophos, acephate and carbofuran were highly mutagenic in lactam test in JK947 strain whereas Allethrin, captan, folpet, monocrotophos |

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| by the Ames and lactam tests<br><br>Hour, T. C. et al. | | | | | | showed weak mutagenicity to JK3 strain Ames test: The six pesticides were more mutagenic to JK947 than TA100 and TA1535 but they were not mutagenic to JK1 or TA98 |
| 64. Genotoxicity of six pesticides by salmonella mutagenicity test and SOS chromotest<br><br>Ruiz, M. J & Marzin, D. | 1997 | Spain | Atrazine, Captan | S. typhi TA1535, TA1537, TA98, TA100 and TA102 | Ames test | Dose related mutagenic effect of captan in all strains both in presence and absence of S9. The others showed no mutagenic activity |
| 65. Mutagenic evaluation of the pesticides captan, folpet, captafol, dichlofluanid and related compounds with the mutants TA102 and TA104 of Salmonella typhimurium<br><br>Barrueco, C. & Pena, E. d. l. | 1988 | Spain | Captan and Folpet | S. typhi TA102 and TA104 | Ames test | Captan and folpet were mutagenic in TA104 strain without S9 mix indicating that they are direct mutagens. |
| 66. Mutagenic activity in synthetic | 1988 | Spain | Resmethrin, Permethrin and Fenvalerate | S. typhi TA1535, TA100, TA1538, | Ames test | No effect in presence or absence of S9 |

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| pyrethroids in Salmonella typhimurium<br><br>Herrera, A. & Laborda, E. | | | | TA98, TA1537, TA97 and TA104 | | |
| 67. Genetic toxicity of a mixture of fifteen pesticides commonly found in the Italian diet<br><br>Dolara, P. et al. | 1993 | Italy | Carbendazim, Thiabendazole, Diphenylamine, Chlorthalonil, Procymidone, Chlorpropham | S. typhi TA153, TA1538, TA98,TA100, TA1535, TA102 | Ames test | No mutagenic activity of mixture |
| 68. Microbiological mutagenicity studies of pesticides in vitro<br><br>Carere, A. et al. | 1978 | Italy | Captan, Dichlorvos, Dodine, Picloram, Triallate | S. typhi TA1535, TA1536, TA1537 and TA1538 | Ames test | Dodine and Picloram had no effect, Captan and Triallate, was seen to be mutagenic in Salmonella (strain TA1535) with and without S9, Dichlorvos and Trichlorfon were negative in the spot test but mutagenic after incubation in liquid cultures of strain TA1535 |
| 69. Mutagenicity of dichlorvos and other structurally related pesticides in Salmonella | 1978 | Italy | Diallate, Dichlorvos, Monocrotophos, Triallate, Trichlorfon | S. typhi-TA1535(missense), TA1536, TA1537 and TA1538 (frame-shift) | Ames test | Dichlorvos and Trichlorfon were negative in the spot test but mutagenic after incubation in liquid cultures of strain |

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| and Streptomyces<br><br>Carere, A. et al. | | | | | | TA1535, Triallate was strongly mutagenic in TA1535, Diallate and Monocrotophos had no effect |
| 70. Mutagenicity of diallate, sulfallate, and triallate and relationship between structure and mutagenic effects of carbamates used widely in agriculture<br><br>Lorenzo, F. D. et al. | 1978 | Italy | Carbaryl, Propoxure, Diallate and Triallate | S. typhi TA1535, TA1537, TA1538, TA98, and TA100 | Ames test | Diallate and triallate is seen to show mutagenicity with liver microsomal fraction on strains TA1535 and TA100, diallate being the most active. No mutagenicity seen in other strains in presence or absence of S9 fraction. Other two pesticides had no effect in any strain |
| 71. Mutagenic activity of phosmet, the active component of the organophosphorus insecticide Decemtione EK 20 in Salmonella and Saccharomyces assays<br><br>Vlckova, V. et al. | 1993 | Slovakia | Phosmet | S. typhi TA97, TA98, TA100, TA1535 and TA1538 | Ames test | No mutagenic activity in strains TA98, TA1535 and TA1538. Dose dependent increase in mutation frequency was seen in strain TA100 and to a lesser extent in strain TA97. |
| 72. Effects of supercypermethrin, a | 1992 | Slovakia | Supercypermethrin | Salmonella typhimurium strains TA1535, | Ames test | No effect in presence or |

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| synthetic developmental pyrethroid, on four biological test systems<br><br>Miadokova, E. et al. | | | | TA100, TA1538, TA98 and TA97 | | absence of S9 mixture |
| 73. Genotoxicity testing of the herbicide Roundup and its active ingredient glyphosate isopropylamine using the mouse bone marrow micronucleus test, Salmonella mutagenicity test, and Allium anaphase-telophase test<br><br>Rank, J. et al. | 1992 | Denmark | Roundup and its active agent, glyphosate isopropylamine salt | S. typhi TA98 and TA100 | Ames test | Weak mutagenic effect in TA98 (without S9) in TA100 (with S9) |
| 74. On the mutagenic and recombinogenic activity of certain herbicides in Salmonella typhimurium and in Aspergillus nidulans | 1988 | Greece | 2,4-D, MCPA, Atrazine | S. typhi TA97a, TA98, TA100, TA1535, TA1537, and TA1538 | Ames test | 2,4-D and MCPA - weak mutagens only in strain TA97a after metabolic activation. Atrazine had no effect |

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| Kappas, A. | | | | | | |
| 75. Lack of mutagenicity of synthetic pyrethroids in Salmonella typhimurium strains and in V79 Chinese hamster cells<br><br>Pluijmen, M. et al. | 1984 | France | Cypermethrin, Permethrin, Deltamethrin, , Resmethrin, and Fenvalerate, | Salmonella typhimurium TAI00 or TA98 | Ames test | No effect in presence or absence of S9 |
| 76. Bacterial mutagenicity investigation of epoxides - drugs, drug metabolites, steroids and pesticides<br><br>Glatt, H. et al. | 1983 | Germany | Dieldrin, Heptachlor epoxide | S. typhi TA98 and TA100 | Ames test | No effect in presence or absence of S9 |
| 77. Activity of organophosphorus insecticides in bacterial tests for mutagenicity and DNA repair — Direct alkylation vs. metabolic activation and breakdown. I. Butonate, vinylbutonate, | 1982 | Germany | Trichlorfon, Dichlorvos | S. typhi tester strain TA1535, TA1537, TA1538, TA98 and TA100 | Ames test | Dichorvos and Trichlorfon Mutagenic towards TA100 indicating base pair mutation. Microsomal enzymes decrease the mutagenic activity |

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| trichlorfon, dichlorvos<br><br>Braun, R. et al. | | | | | | |
| 78. Chemical induction of streptomycin-resistant mutations in Escherichia coli. Dose and mutagenic effects of dichlorvos and methyl methanesulfonate<br><br>Wild, D. | 1972 | Germany | Dichlorvos | E. coli B | E. coli were grown on medium containing dichlorvos and streptomycin | Dichlorvos increased streptomycin resistant mutants in the bacteria |
| 79. Mutagenic activity of diallate and triallate determined by a battery of in vitro mammalian and microbial tests<br><br>Douglas, G. R. et al. | 1981 | Canada | Diallate and Triallate | S. typhi TA1535, TA1537, TA1538, TA98, and TA100 | Ames test | Dose-related increases in strains TA1535 and TA100 in the presence of S9 for both pesticides. Higher concentration of the pesticides leads to mutation in TA98 with S9. No mutagenic effect was found in strain TA1537 or TA1538 for either compound |
| 80. The mutagenic activity of 61 agents as determined by the micronucleus, | 1979 | Canada | DDT | S. typhi TA1537, TA98, and TA100 | Ames test | No effect in presence and absence of S9 |

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| Salmonella, and sperm abnormality assays<br><br>Bruce, W. R & Heddle, J. A. | | | | | | |
| 81. Mutagenicity of dichlorvos<br><br>Smith, M. J. A. et al. | 1972 | Canada | Dicholrvos | E. coli WP2 ($Trp^-$) | Ames test | The compound was mutagenic |
| 82. An evaluation of 6 short-term tests for detecting organic chemical carcinogens<br><br>Purchase, I. F. H. et al. | 1978 | UK | DDT, Dieldrin | S. typhi TA98, TA100, TA1535, TA1538 | Ames test | No effect in presence or absence of S9 |
| 83. The Mutagenic Effects of Organophosphorus Pesticides on Microorganisms<br><br>Dean, B. J. | 1972 | UK | Dichlorvos, Malathion, Monocrotophos | Escherichla coli WP 2, | Ames test | All negative in E.coli, Dichlorvos produced a significant, dose-related increase in the number of revertants at each concentration |
| 84. BHA, BHT And Ethoxyquin Tested for Mutagenicity<br><br>Joner, P. E. | 1977 | Norway | BHA, Ethoxiquin | S. typhi TA1535, TA1537, TA1538, TA98, and TA100 | Ames test | No effect in presence or absence of S9 |

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| 85. The mutagenicity of MCPA and its soil metabolites, chlorinated phenols, catechols and some widely used slimicides in Finland<br><br>Rasanen, L. et al. | 1977 | Finland | MCPA and Its Soil Metabolites, Chlorinated Phenols, Catechols | S. typhi TA98, TA100, TA1535, TA1537 | Ames test | No effect in presence and absence of aroclor induced wisteria rat liver homogenate S9 |

# Chapter 3

# Results

## 3.1 Study selection

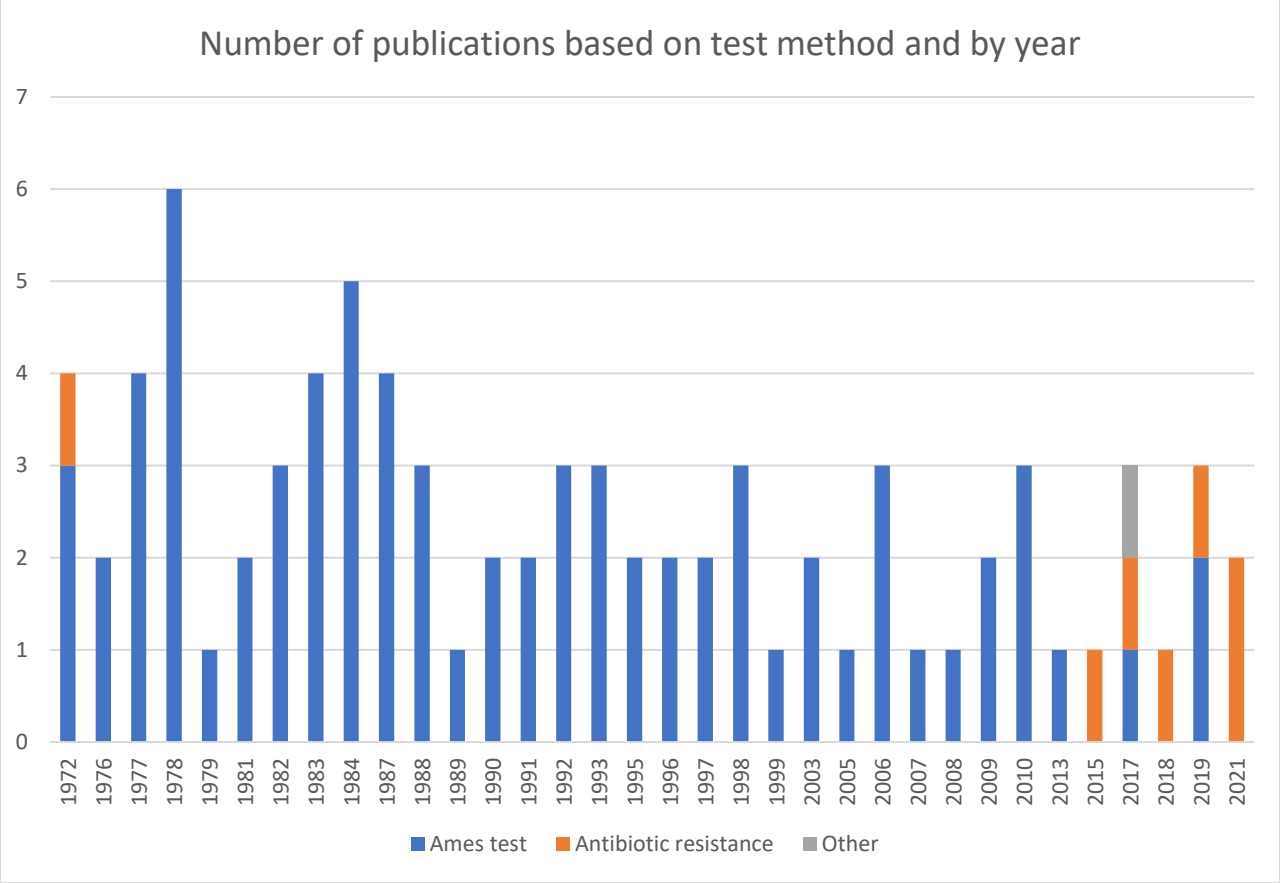


**Figure 2: Bar chart representing number of publications based on test method and by year**

**Note:** For the "other" category, only one test method was found which was the genome wide mutagenesis test utilizing whole genome sequencing.

The systematic search identified 5889 publications after all the duplications were removed by using the previously described search strategy. Among these studies, only 165 articles were included for full text screening. Review papers and publications not meeting the inclusion criteria were excluded. Finally, 85 articles were included in the systematic review. The earlies publications were from the year 1972. Articles primarily focused on laboratory investigations. All relevant

studies tested mainly two species of enteric pathogenic bacteria – *Salmonella typhimurium* and *Escherichia coli.* Addition articles were searched from the reference section of included studies.

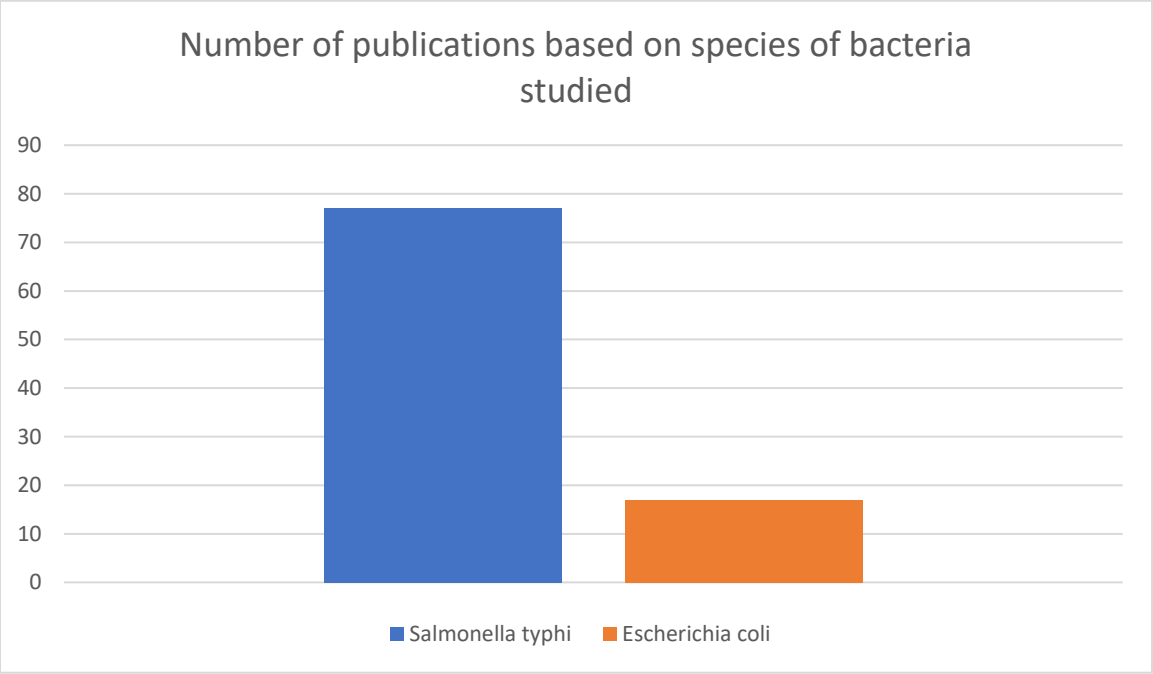


**Figure 3: Bar chart representing number of publications based on species of bacteria studied**

### 3.2 Pesticides assessed in the investigation

Out of the 85 publications selected, 44 publications studied insecticides, 37 publications studied herbicides and 24 publications studied fungicides. Almost all of the studies examined pesticides individually. Only two publications studied two or more pesticide mixtures (Plewa et al., 1984; Dolara et al., 1993). Inert ingredients which are included in the pesticide formulations were studied in one publication (Kurenbach et al., 2017). Some publications used the metabolites of pesticides instead of the actual pesticide (Rasanen et al., 1977; Sueferer, 1978; Butler & Hoagland, 1989; Bajpayee et al., 2006; Nelson et al., 2009).

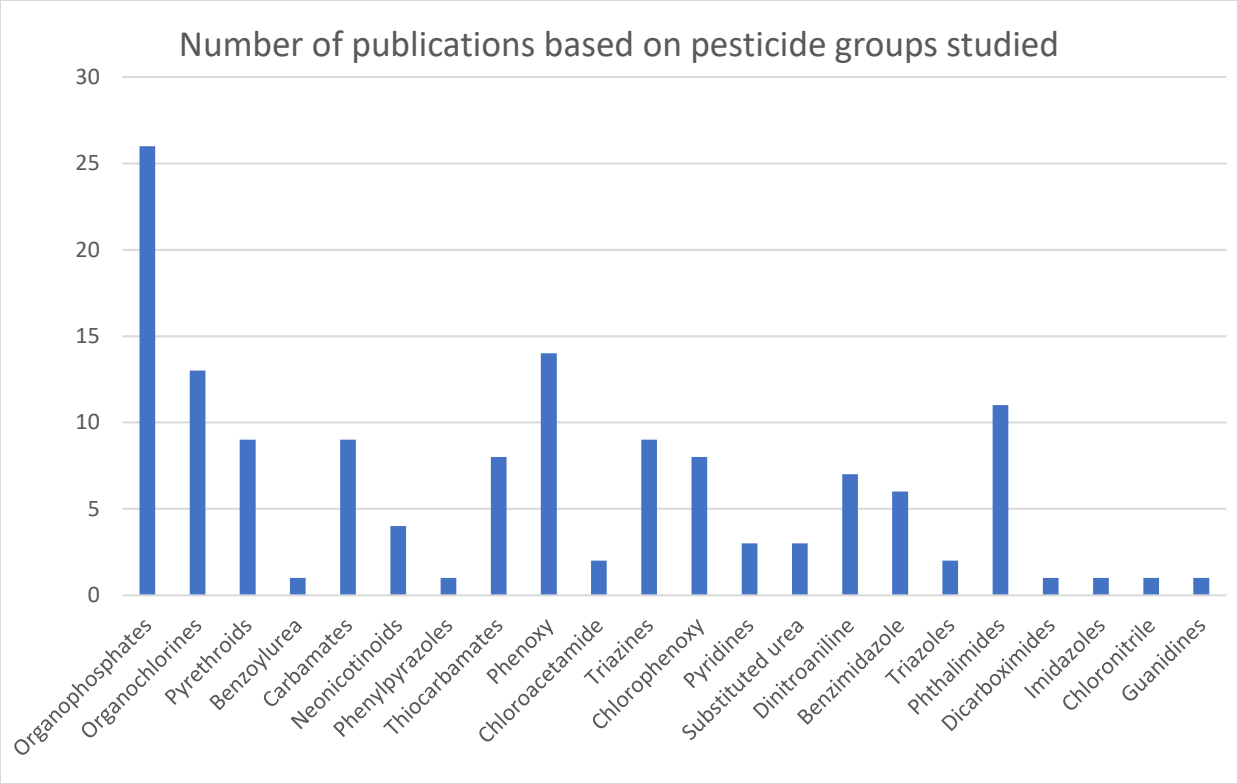


**Figure 4: Bar chart representing number of publications based on pesticide groups studied**

### 3.2.1 Insecticides

44 publications that included insecticides investigated the mutagenic effects of 38 insecticides. The insecticide groups most studied were organophosphates (16 insecticides investigated), followed by pyrethroids (7 insecticides), organochlorines (6 insecticides), carbamate (5 insecticides). Neonicotinoid (2 insecticides), benzoylurea (1 insecticide), phenylpyrazol groups (1 insecticide) were the least studied insecticide group. Among the 38 insecticides, Dichlorvos was the most studied insecticide (10 publications) followed by carbofuran and malathion (5 publications), DDT, Dieldrin, Chlorpyrifos, Permethrin, Diazinon and Carbaryl (4 publications). Technical grade of the pesticides was evaluated more compared to the commercial formulations. However, some articles did not specify the configuration of the pesticide examined.

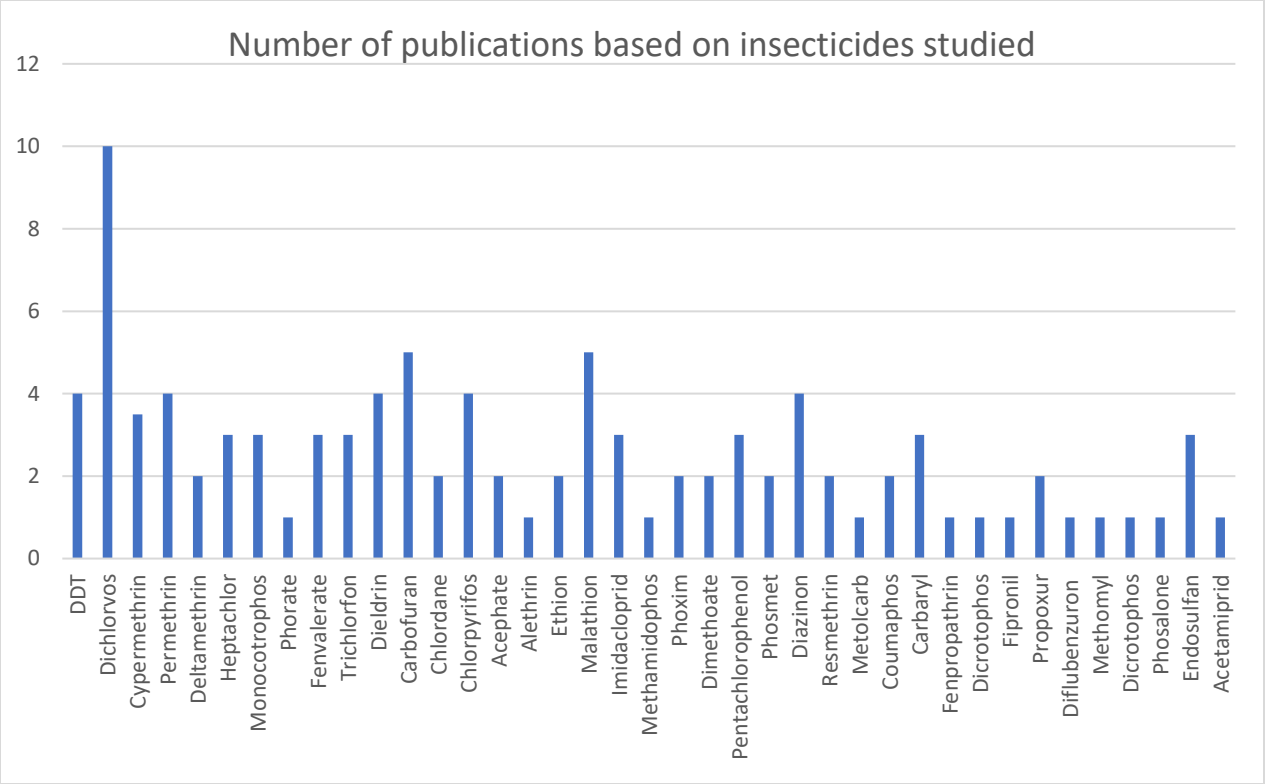


**Figure 5: Bar chart representing number of publications based on insecticides studied**

### 3.2.2 Herbicides

The 37 publications that evaluated herbicides investigated the mutagenic effects of 25 herbicides. The herbicide groups mainly studied were thiocarbamates (2 herbicides), Chloroacetamide (2 herbicides), Phenoxy group (2 herbicides), Substituted urea (2 herbicides), Dinitroaniline (2 herbicides), followed by phenoxyacetic acid, triazine, phenylurea which were the least studied groups. The most commonly studied herbicides were 2,4-D and Triallate (8 publications), followed by glyphosate (7 publications), Diallate (6 publications), Atrazine and Trifluralin (5 publications), Dicamba, MCPA and Linuron (4 publications). Commercial formulations of the pesticides were studied more compared to the technical grade. Few studies did not mention the format of the pesticide used.

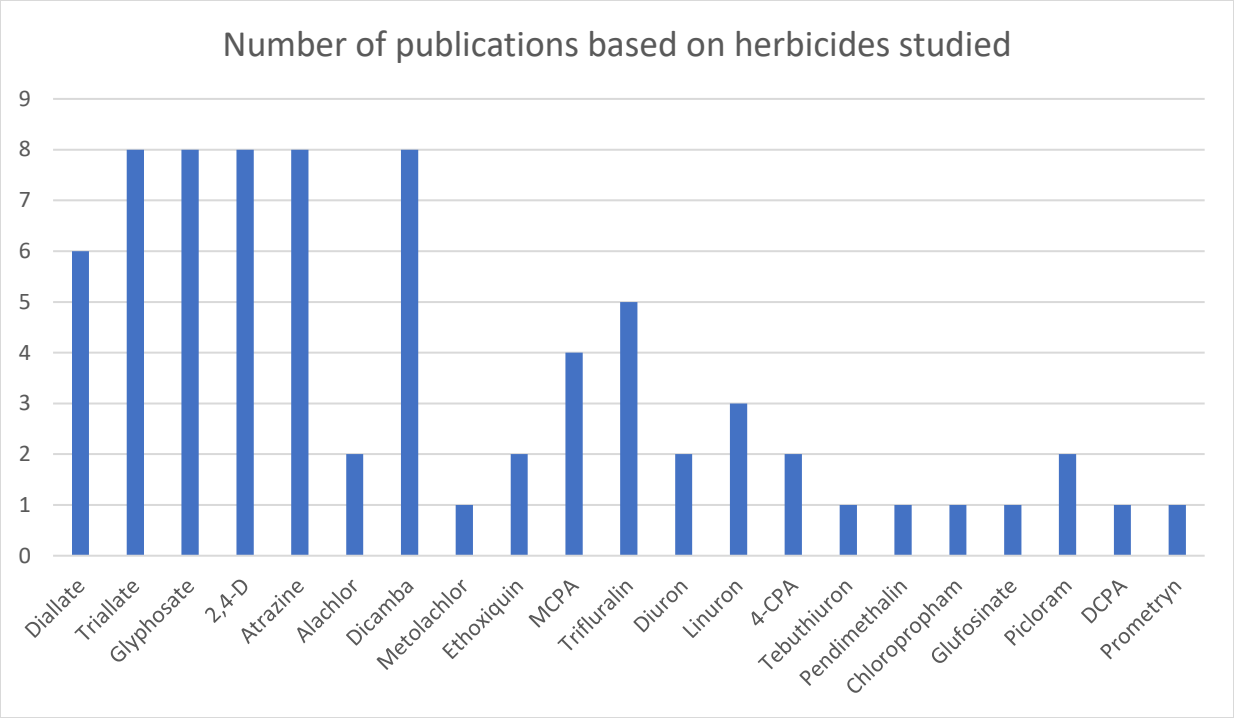


**Figure 6: Bar chart representing number of publications based on herbicides studied**

### 3.2.3 Fungicides

The mutagenic effects of 14 fungicides were investigated. The most widely used fungicide groups were Azole fungicides which included triazole class (5 fungicides), benzimidazole class (2 fungicides), Imidazole class (1 fungicide) of fungicides. These were followed by phthalimide class (2 fungicides), dicarboximides (1 fungicide). Captan was the most studied fungicide with 12 publications, and then thiabendazole (5 publications), carbendazim and folpet (4 publications), chlorothalonil (3 publications), imazalil (2 publications) were examined. Technical grades were investigated more than commercial grades. Only a few articles did not specify the test compound configuration.

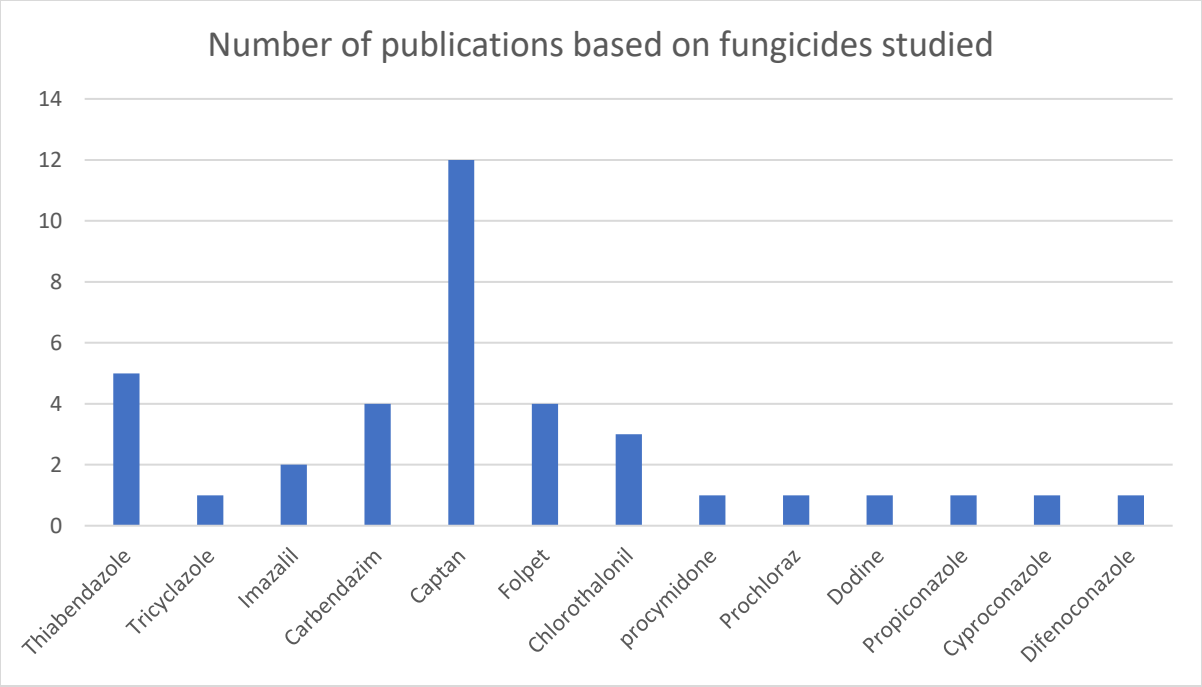


**Figure 7: Bar chart representing number of publications based on fungicides studied**

### 3.3 Effects of Pesticides Tested on Bacterial Species

#### 3.3.1 Ames Test

The Ames Test is a mutagenicity test where modified strains of S. typhi and E. coli are used whose ability to synthesize histidine and tryptophan are removed respectively. The test is performed to see whether the test compound can revert the auxotrophic strain back to its prototrophic state by observing their growth in the particular amino acid (histidine or tryptophan) free medium. In most cases, liver metabolism system (rat) and in some cases plant metabolism systems are used because often times, not the pesticides themselves but their metabolites can be mutagenic as well.

The Ames test was performed in 77 publications and among these, 74 publications investigated *S. typhi* tester strains (TA97, TA98, TA100, TA1535, TA1536, TA1537, TA1538, TA102, TA104). Each strain has either a base-pair substitution or frame shift mutation by which their histidine synthesis ability is removed. We found 67 articles that tested for base pair mutations (TA100, TA1535, TA102, TA104) and 65 articles that studied frameshift mutations (TA98, TA1536, TA1537, TA1538). On the other hand, among the 81 publications that included Ames test, only 9

publications investigated the effects of pesticides on E. coli tester strain (WP2) which has a base pair substitution mutation that removes its' ability to synthesize tryptophan. Most of the studies included liver metabolism systems of rats (70 publications) and a few studies utilized plant metabolism system (10 publications).

Among the pesticides tested, the studies retrieved investigated 10 herbicide classes, 7 insecticide classes and 4 fungicide classes. Many publications concluded that dichlorvos, captan, folpet, diallate, triallate were the most mutagenic to these bacterial species by being able to revert back to their prototrophic state (Braun et al., 1982; Hour et al., 1998; Dean, 1972; Carere et al., 1978; Sandhu et al., 1983; Douglas et al., 1981; Moriya et al., 1982). The pesticides that were not found to be mutagenic in general included 2,4-D, trifluralin, glyphosate, DDT, carbaryl (Uysal et al., 2010; Mortelmans et al., 1984; Purchase et al., 1978; Zeiger et al., 1992; Li et al., 1987; Franco-Bernardes et al., 2017).

Very few studies investigated the effects of pesticide mixtures and pesticides with other chemicals. Out of these studies, one study displayed the synergistic effect between two commercial grade herbicides (metolachlor and atrazine) in the presence of a plant metabolism system (Plewa et al., 1984). Another study involving mixtures of several pesticides had no mutagenic effect on S. typhi (Dolara et al., 1993). Pentachlorophenol was able to show synergism with a synthetic arylamine, 2-AF and also with a carcinogenic derivative of fluorine (2-AAF) by increasing their ability to induce base-pair and frameshift mutations (Gichner et al., 1998). BHA, an antioxidant used in pesticide formulations was shown to decrease the mutagenicity of a carcinogenic aromatic amine, 3,2-dimethyl-4 aminobiphenyl, IQ, MeIQ and MeIQx indicating an antagonistic relationship (Chen et al., 1991; Reddy et al., 2009).

### 3.3.2 Effects on Antibiotic Resistance

Only 7 publications were found that reported the effect of pesticides on antibiotic resistance. Similar to the Ames test, antibiotic resistance was also primarily investigated in *Salmonella typhimurium* and *Escherichia coli*. Out of the 7 publications, 5 publications studied herbicides, 2 publications studied insecticides, 1 publication investigated a fungicide. Environmental relevant concentrations of herbicides were noted in 4 studies and the other studies did not specify the relevance to the environment. Among these, 3 studies used commercial formulations of herbicide (Kurenbach et al., 2015; Kurenbach et al., 2018; Jun et al., 2019), 3 studies used pure active

ingredients (Kurenbach et al., 2017; Li et al., 2021; Wild, 1972), one study utilized inactive ingredient (co-formulants) (Kurenbach et al., 2017) and one study did not specify the configuration of the pesticide used (Guo et al., 2021). In these studies, the most commonly studied antibiotics were tetracycline (6 publications), followed by ampicillin and kanamycin (5 publications), ciprofloxacin and streptomycin (4 publications) and chloramphenicol (3 publications).

Effects of pesticides on the tolerance to different antibiotics were observed in 5 publications. Also, 4 publications were found to examine pesticide induced changes in MIC of the antibiotics and alteration in expression pattern of genes resulting in susceptibility to antibiotics. Only 2 publications investigated the horizontal transfer of antibiotic resistance genes (ARG) induced by pesticides utilizing E. coli HB101 and E. coli DH5α as donor and recipient. These studies showed that pesticides could increase the conjugative transfer of ARGs between recipient and donor by enhancing the expression of pilus genes, increasing outer membrane protein gene expressions thus enhancing cell membrane permeability and increasing secretion of Extracellular Polymeric Substance content. Generally, the effects observed depended on pesticides, antibiotics and the species studied.

### 3.3.3 Genome Wide Mutagenesis Test

Only one study was found to investigate whether the pesticide could induce a genome wide mutation in bacteria utilizing the whole genome sequencing (WGS) method (Tincher et al., 2017). The pesticide tested in this study was glyphosate Roundup which contains the herbicide, glyphosate and it was evaluated in field relevant concentrations. Escherichia coli was used as the test organism and it was found that long exposure to the herbicide had no effect on mutation rate of base pair substitution, transposable elements or gene duplication. As a result, the study came to a conclusion that glyphosate has no effect on bacteria.

# Chapter 4

## Discussion

The findings of this review reveal that pesticides can be mutagenic in bacteria with insecticides, namely organophosphate insecticides being seen to be mutagenic in almost all studies tested. One of the possible reasons for their mutagenic property can be because of the fact that these organophosphate insecticides are considered to be alkylating agents which play a role in causing mutations (Wooder & Wright, 1981). Among the organophosphates, dichlorvos were studied the most and it displayed mutagenic responses in bacteria in all studies tested. Studies have reported dichlorvos as having alkylating properties which can support the claim that it is a mutagen (Segerbäck & Ehrenberg, 1981). Another explanation of the mutagenicity of dichlorvos can be given in regards to their chemical structure. Dichlorvos contains vinyliden chloride group in its structure which is a known mutagen that can contribute to the mutagenic activity of the pesticide (Carere et al., 1978; Fabricant & Legator, 1981).

In general, no herbicide tested was significantly mutagenic except for the thiocarbamate herbicides, diallate and triallate. It is hypothesized that these herbicides contain a chemical group called allyl chloride which may be responsible for the mutagenic action of these pesticides as alyl chloride is similar in structure to vinyliden chloride (Carere et al., 1978). Among the fungicides studied, captan and folpet were notably the most mutagenic in bacteria possibly attributing to their similar chemical structure (Gordon et al., 2010). The mutagenic ability of pesticides can also be supported by the fact that these compounds are also known to induce a high amount of reactive oxygen species (ROS) which can ultimately lead to the induction of oxidative stress (Rasheed et al., 2022). These findings suggest that structural and functional properties may contribute to the mutagenic role of pesticides.

The results of this study also present that these mutations came in the form of base-pair substitutions or frameshift mutations. Though the test is performed utilizing the histidine operon in *Salmonella typhimurium* and the tryptophan operon in *Escherichia coli*, it can be hypothesized that these pesticides can cause mutation in other bacterial genes in a similar mechanism via transitions, transversions, deletions, insertions. One of the probable reasons behind this is that alkylating agents can cause mutations by base mispairing which leads to mainly GC to AT

transitions (Jenkins et al., 2005). Furthermore, reactive oxygen species (ROS) are also reported to induce GC to AT transitions in DNA (Markkanen, 2017). In addition to that, some studies have reported that ROS can also reduce MMR activity which leads to the induction of frameshift mutations (Skinner & Turker, 2005).

Most studies included in this scoping review also tested pesticide mutagenicity by incorporating a mammalian and plant metabolic system. Though there is no presence of a mammalian or plant metabolic system in bacteria, it can be hypothesized that the pesticides can be metabolised through the mammalian system and affect the intestinal microbiota or pathogens residing in the human body. Also, as almost all plants are exposed to pesticides, these substances can be metabolised through the plant metabolic system and cause mutations to the bacteria located on or near the plants. In fact, many studies have reported the presence and survival of human enteric pathogens like *E. coli* and *Salmonella* on plants (Lim et al., 2014).

The few studies involving antibiotic resistance have showed that it is possible for pesticides to reduce the susceptibility of clinically relevant drugs. These studies also showed the effect pesticides had on efflux pumps. Markedly, pesticides were seen to induce the overexpression of the resistance nodulation division (RND) family efflux pump, AcrABTolc. These efflux pumps have been proved to be linked to inducing resistance to several antibiotic classes such as carbapenem, fluoroquinolone, tetracyclines, aminoglycosides (Chetri et al., 2019; Swick et al., 2011; Takatsuka et al., 2010). Pesticides are also found to induce horizontal gene transfer (HGT) in *E. coli* that promotes transfer of Antibiotic resistance genes (ARG). This implies that pesticides can contribute to plasmid mediated gene transfer between the same species or even different species. This is a serious concern in that ARGs can be transferred from one pathogen to another pathogen or even from soil bacteria to a pathogen. Indeed, some studies have reported the discovery of novel ARGs found in soil bacteria (Lau et al., 2017). These ARGs can conceivably transfer to clinical pathogens at a rapid rate in the presence of pesticides.

While this study highlights a serious issue that has been overlooked, it has a few limitations as well. All of the publications included here focused on only two species of enteric pathogens. As a result, effects of pesticides on the other pathogens could not be tested. Furthermore, most articles utilized the Ames test which uses modified strains of the bacteria in which the bacteria are devoid of lipopolysaccharide that helps increase permeability to the chemicals being tested. However, the

wild type strains do not have these modifications. As such, no definitive conclusion can be made in respect to the wild type strains. The studies testing for antibiotics are also challenging to interpret as there is only a limited number of investigations utilizing very few pesticides and only two species of bacteria ultimately resulting in insufficient data.

# Chapter 5

# Conclusion

To the best of our knowledge, this is the first scoping review on the mutagenic effects of pesticide on enteric pathogens. Our findings point out that pesticides, especially organophosphate insecticides, thiocarbamate herbicides (diallate and triallate), phthalimide fungicides (captan and folpet) have the potential to cause base-pair substitution and frameshift mutations. Although most of the articles discussed here investigated with modified strains of the bacteria, it can only be assumed that the same effect will occur in the wild type strains. Moreover, the studies testing for association between pesticides and antibiotic resistance have shown a positive correlation.

As pesticides are widely used in a large number, they can easily pollute the soil and aquatic ecosystems where several pathogens may inhabit. Also, the soil can be contaminated with antibiotics which can, in combination with the pesticides lead to antibiotic resistance. Therefore, the findings of this review are significant in that it can help in evaluating the risk assessment of pesticides in the environment along with the usual toxicological effects studied. It also broadens our knowledge regarding the current antibiotic resistance crisis and possible environment pollutants that may lead to the evolution of resistance.

Future research should delve further into the mutagenic aspect of pesticides, particularly studying the effect on wild type strains. The synergistic effect between pesticides and other environmental contaminants such as heavy metals, surfactants, biocides etc should be studied as these compounds are also linked to antibiotic resistance (Buelow et al., 2021). Furthermore, genome wide mutagenesis test with whole genome sequencing should be investigated for other widely used pesticides besides glyphosate such as chlorpyrifos, dichlorvos, 2,4-D etc. While testing pesticides individually is important, it is equally vital to investigate pesticide mixtures as pesticide mixtures are frequently found in the environment and they may also induce a different mutagenic effect than when tested alone. Other than the certain herbicides used in the selected publications, further research on antibiotic resistance should also include relevant insecticides and fungicides.

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