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1   Transgenerational effects of insecticides - implications for rapid pest evolution in

2   agroecosystems

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Highlights

14 • Insecticide-induced effects can be transgenerationally inherited.

15 • Epigenetic modifications are heritable.

16 • Epigenetic modifications are responsive to insecticide-induced stress.

17 • Pesticide use may directly and indirectly drive the evolution of insect pests in

18 agroecosystems via epigenetic processes.

Abstract

20 Although pesticides are a major selective force in driving the evolution of insect pests,

21 the evolutionary processes that give rise to insecticide resistance remain poorly understood.

22 Insecticide resistance has been widely observed to increase with frequent and intense insecticide

23 exposure, but can be lost following the relaxation of insecticide use. One possible but rarely

24 explored explanation is that insecticide resistance may be associated with epigenetic

25 modifications, which influence the patterning of gene expression without changing underlying

26 DNA sequence. Epigenetic modifications such as DNA methylation, histone modifications, and

27 small RNAs have been observed to be heritable in arthropods, but their role in the context of

28 rapid evolution of insecticide resistance remain poorly understood. Here, we discuss evidence

29 supporting how: 1) insecticide-induced effects can be transgenerationally inherited, 2) epigenetic

30 modifications are heritable, and 3) epigenetic modifications are responsive to pesticide and

31 xenobiotic stress. Therefore, pesticides may drive the evolution of resistance via epigenetic

32 processes. Moreover, insect pests primed by pesticides may be more tolerant of other stress,

33 further enhancing their success in adapting to agroecosystems. Resolving the role of epigenetic

34 modifications in the rapid evolution of insect pests has the potential to lead to new approaches

35 for integrated pest management as well as improve our understanding of how anthropogenic

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Transgenerational effects on pest evolution

36   stress may drive the evolution of insect pests.

3

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Introduction

39   The pesticide treadmill describes how agricultural insect pests evolve resistance in

40   response to frequently used pesticides, rendering them ineffective. Pesticides are pervasive in

41   agriculture, and are a major selective force driving the evolution of insect pests in

42   agroecosystems [1]. Although insecticide resistance has been documented in a wide range of

43   insect pests [2] and the genetic basis of major gene resistance has been mapped in key pests for

44   select insecticides [3], the broader evolutionary processes that give rise to insecticide resistance

45   remain poorly understood [4,5]. Farmers and entomologists have observed that insecticide

46   resistance increases with the frequency of exposure to particular insecticides [6–8], but can be

47   lost following the relaxation of insecticide use [9–11]. The rapid gain and loss of resistance

48   appears to occur far more rapidly than expected based upon mutation rates [12,13], suggesting

49   that insecticides themselves may increase the rate of mutation or cause physiological changes in

50   pest organisms [5]. One possible explanation that has been relatively unexplored is that the

51   evolution of insecticide resistance results from epigenetic modifications, which are heritable and

52   influence gene expression without changing the underlying DNA sequence.

53   The evolution of insecticide resistance has been considered an evolutionary paradox [5],

54   in that pest species which have experienced repeated genetic bottlenecks due to invasion and

55   selection remain able to adapt very rapidly, despite limited genetic diversity. The same insect

56   pests have evolved resistance to insecticides in all of the major classes [14], and are expected to

57   evolve resistance to future chemistries [15]. Extreme genetic bottlenecks also do not appear to

58   limit the likelihood that insecticide resistance evolves. For example, all Colorado potato beetle

59   (*Leptinotarsa decemlineata* Say) populations in Europe are descended from the introduction of a

4

60   single female, or single mtDNA haplotype [16]. Despite this strong historic bottleneck, *L.*

61   *decemlineata* populations in Eurasia have evolved resistance to a wide range of insecticides in

62   Europe, the Middle East, and East Asia [6,17,18]. There is a seeming inevitability of insecticide

63   resistance developing in pests, where new phenotypes arise following environmental stress at

64   rates that may not be explained by natural selection. Indeed, Skinner et al. [19] argued how

65   epigenetic processes fit within a neo-Lamarckian framework, because environmental epigenetic

66   patterning can influence transgenerational transmission of phenotypic variation. By influencing

67   epigenetic modifications, xenobiotic and environmental stressors can directly influence the

68   phenotypic responses of organisms to their environment.

69   Epigenetics is the field of study that examines how environmental factors influence

70   heritable changes in gene expression. There are several epigenetic mechanisms that are heritable

71   and could underlie transgenerational effects of insecticides: DNA methylation [20], histone

72   modifications [21], and heritable noncoding RNA [22]. Here, we discuss evidence supporting

73   how 1) insecticide-induced effects can be transgenerationally inherited, 2) epigenetic

74   modifications are heritable, and 3) epigenetic modifications are responsive to insecticide-induced

75   stress. We draw on other model systems from a diverse body of literature, including genetics,

76   epigenetics, and toxicology to identify gaps in our understanding around the evolution of

77   insecticide resistance in insect pests. We close with a discussion of the implications of epigenetic

78   processes for insect fitness in intensively-managed agroecosystems.

79

80   **Insecticide-induced hormetic effects can be heritable**

81   Insecticides not only select for insecticide resistance and point mutations at target sites,

82   but they can also affect physiological and life-history traits [23]. In particular, exposure to

5

83 sublethal dosages of insecticides can incur stress and lead to increased phenotypic variation [24].

84 Stress responses can lead to hormesis, a well-known phenomenon from toxicological literature,

85 where small dosages can stimulate biological functions whereas large dosages are detrimental or

86 lethal [24]. Hormetic responses include activation of stress response pathways in a variety of

87 taxa from microbes, plants, and animals. They are not related to any special class of compounds,

88 as hormetic effects have been reported for over 240 different chemical classes [23]. Sublethal

89 exposure to insecticides can induce hormetic effects and lead to variety of positive life history

90 effects, such as mating success [25], fecundity [26], and body size [27]. By positively

91 influencing traits associated with fitness, hormetic effects may play an important role in pest

92 evolution.

93   There is evidence that individuals exposed to stressful conditions, either abiotic or biotic,

94 can prime gene expression in their offspring to be able to better tolerate stress [28,29].

95 Insecticides have been shown to induce transgenerational insecticide induced hormetic effects,

96 but thus far the results have been difficult to interpret. For example, *Myzus persicae* aphids

97 treated with sublethal levels of imidacloprid produce offspring that survive longer when exposed

98 to food/water stress, but tolerance to insecticide stress is unchanged [30]. Similarly, although

99 sublethal levels of precocene (an antagonist to Juvenile hormone) stimulate reproduction in *M.*

100 *persicae,* the results are not passed on to subsequent generations [31*]. Although chemical-

101 induced hormesis has been reported from many groups and these changes have also been

102 reported to be inherited [23] the genetic, epigenetic, and toxicological basis of hormesis is still

103 poorly understood [5,32].

104

105 **Epigenetic modification and transgenerational inheritance**

6

106   Epigenetic modifications have been shown to be heritable [20]. DNA methylation, the

107   addition of a methyl group to the 5 carbon position of cytosine a nucleotide (usually the cytosine

108   in CpG dinucleotides), is a well-documented mechanism of epigenetic inheritance that can

109   influence phenotypic variation (Table 1), and is found in most, if not all, orders of insects [32].

110   Methylation in insects is largely found within coding regions, and is closely linked with gene

111   expression and alternative splicing - where a single gene can generate a diversity of gene

112   transcripts of differing length, based on which exons are translated [33]. Methylation can occur

113   at any location in the genome, but the effects of DNA methylation vary based on its location in

114   the genome (Figure 1): A) changes in DNA methylation at the promoter region can influence

115   gene expression in downstream genomic regions [34], B) methylation suppresses gene

116   expression of transposable elements (TEs, which are mobile genetic elements responsible for the

117   majority of mutations in many genomes) and prevent TE mobilization [35], and C) Gene body

118   methylation can increase gene expression [32], as well as an increase in the number of alternative

119   splice variants [36]. Changes in methylation patterns in arthropods can be associated with

120   changes in levels of resistance to insecticides. *Myzus persicae*, can gain insecticide resistance

121   through the duplication of esterase genes and subsequent overexpression of esterases [37]. After

122   suspending insecticide exposure, extra copies of esterase genes can be methylated, leading to a

123   loss of resistance. It is possible that these aphid populations could quickly become resistant again

124   following demethylation of these amplified genes.

125   Histone modifications include additions of acetyl or methyl groups on the histone

126   proteins around which nuclear DNA is wrapped, which can influence gene regulation and

127   expression [38]. The full effects of these modifications are not well known, especially in

128   arthropods. However, it does appear that some histone modifications are able to be transmitted

7

129   transgenerationally [39]. Different noncoding RNA (ncRNA) [22] can be inherited through either

130   the male or female gametes, though most current research does not incorporate analysis of

131   heritable RNA. Certain types of small RNA can direct and maintain DNA methylation and

132   histone modification, and therefore affect chromatin structure [40]. DNA methylation, histone

133   modifications, and ncRNAs form a constellation of interacting effects that result in a phenotypic

134   response [41]. To fully understand how epigenetic modifications influence transgenerational

135   phenotypic inheritance, it would be optimal to assess all three mechanisms simultaneously

136   through concurrent small RNA-seq, bisulfate-treated DNA-seq, and histone modification assays,

137   in as many tissues and individuals as possible. Ideally, multiple generations would be sequenced,

138   to determine if changes in epigenetics and gene expression differ consistently between

139   treatments. Because the cost of sequencing is the major limiting factor for these studies,

140   projected lower sequencing costs in the future should enable these types of studies.

141

142   Epigenetic modifications are responsive to xenobiotic stress

143   Exposure to insecticides and other xenobiotic compounds can alter DNA methylation

144   status in arthropods, and these epigenetic changes can persist for at least several generations

145   [20,42,43]. Table 1 lists a number of examples of stress leading to epigenetic changes in

146   arthropods. Studies focusing on insects are few in number, so our scope is broadened to include

147   examples from aquatic ecotoxicology literature, which includes a number of non-insect

148   arthropods. Oppold (2015) found that exposure of mosquitoes to a fungicide leads to heritable

149   changes in methylation and decreases in sensitivity to imidacloprid, an insecticide. Methylated

150   cytosines also spontaneously deaminate, becoming thymines, at a higher rate than non-

151   methylated cytosines, which can lead to higher mutation rates in methylated regions [44]. If

8

152 genes that are associated with resistance are methylated, which leads to increased expression and

153 increased mutation rate, then genes that are most upregulated in response to insecticide resistance

154 may also be the most likely to experience spontaneous deamination.

155 Both the role of histone modifications and small RNA in modifying epigenetic responses

156 to toxins are less understood than DNA methylation in arthropods, though it has been shown that

157 methylation and histone modifications tend to be co-located in the genome [38]. Kishimoto et al.

158 [45*] showed that parental hormetic responses to oxidative stress can be epigenetically

159 transmitted to descendants via histone modifications. A wide range of environmental chemicals,

160 such as heavy metals, air pollutants, dioxins, and endocrine disrupters, can alter histone

161 modifications [46], but it is unknown whether these changes are heritable. We have not found

162 any studies on arthropods examining if insecticides can induce transgenerational small RNAs

163 responses. Small RNAs have been found to interact with histone modifications [47], so changes

164 in small RNAs may be implicated in the transgenerational inheritance of stress phenotypes as

165 well.

166

167 **Implications for transgenerational effects on insect fitness in agroecosystems**

168 We hypothesize that pesticide use can directly and indirectly drive the evolution of insect

169 pests in agroecosystems via epigenetic processes (Figure 2). Pesticides may directly stimulate the

170 expression of advantageous phenotypes, which may be underwritten by epigenetic modifications.

171 Continued insecticide use on populations developing resistance would thus operate as 'natural

172 selection' and selectively increase the frequency of insect phenotypes that are adaptive to

173 pesticides. Indirectly, pesticide use may maintain stressful environments that hormetically prime

174 insect pests to become more tolerant of stressful conditions. For instance, sublethal exposure to

9

175 insecticides can influence adult body size of the *L. decemlineata* [23], which may allow insect

176 pests to be better able to tolerate overwintering conditions [48]. Insecticides can also increase

177 female fecundity [49] or propensity to mate [25], which can increase population size.

178   The phenotypic traits of insect pests that allow them to thrive under insecticide exposure

179 may also facilitate global invasions. For example, *L. decemlineata* is a globally-invasive pest that

180 is expanding its range northwards into the Arctic Circle [48]. Insecticide exposure appears to

181 stimulate the beetle to invest more in fat bodies and have a higher metabolic rate than control

182 beetles [50]. While the higher metabolic rate and larger fat bodies may enable beetles to better

183 detoxify chemicals, higher fat body reserves enable small individuals to overwinter successfully

184 [51,52]. For example, sublethal applications of the pyrethroid deltamethrin on resistant *L.*

185 *decemlineata* populations can have stimulatory effects rendering exposed individuals larger

186 which is also inherited to the next generation (Lindström, unpublished data).

187   To date, most of the research examining the role of pesticides or xenobiotics in epigenetic

188 change come from the field of aquatic toxicology [53**], where environmental exposure to

189 toxins can be highly variable and difficult to predict. In contrast, pesticide use in agroecosystems

190 is intentionally part of an active pest management system, where insect responses to stresses can

191 cause positive feedbacks on subsequent management decisions. Agroecosystems are also highly

192 controlled systems, which allows for greater experimental control for field and landscape level

193 studies. Along these lines, it would be important to know how epigenetic responses to the same

194 insecticides may vary among individuals, populations, and species. Such information would help

195 provide insight on whether epigenetic responses can be broadly predictable across individuals

196 and species, and possibly, how pesticide resistance may be better managed. A combination of

197 new genomic tools, epigenetic assays, and computationally-intensive approaches may allow us to

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198 better understand to what extent epigenetic responses within insects help drive the pesticide

199 treadmill.

200

201 **Acknowledgements**

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379 Table 1. Examples of epigenetic alterations following exposure to anthropogenic and "natural",
380 (non-anthropogenic) stress.

	Species	Treatment	Phenotypic Effects	DNA Methylation	Histone Modifications	Transgenerational effect	Reference
anthropogenic stressors	*Daphnia magna*	vinclozolin (fungicide)	body size	reduced methylation	n/a	N	[20]
	Daphnia magna	5-azacytidine (demethylating agents)	reproduction, body size	reduced methylation	n/a	Y	[20]
	Myzus persicae (Green Peach Aphid)	imidacloprid (insecticide)	changes in gene expression, including heat shock protein	increased, decreased, or no change based on concentration	n/a	Y	[31*]
	Aedes albopictus (Asian Tiger Mosquito)	genistein (phytohormone)	decrease in sensitivity to imidacloprid	cautious decrease	n/a	Y	[54]
	Aedes albopictus (Asian Tiger Mosquito)	vinclozolin (fungicide)	decrease in sensitivity to imidacloprid	cautious increase	n/a	Y	[54]
"natural" stressors	*Artemia* sp. (brine shrimp)	heat stress	increased Hsp70 production, heat tolerance, and resistance vs. pathogens	changes in methylation	histones H3 and H4 acetylation	Y	[55]
	Daphnia magna	zinc	changes in gene expression	reduced methylation	n/a	Y	[56*]
	Daphnia magna	toxic cyanobacterium *Microcystis aeruginosa*	n/a	differential methylation primarily in exonic regions, enriched for serine/threonine amino acid codons and genes related to protein synthesis, transport and degradation, in genes susceptible to alternative splicing in response to Microcystis stress	n/a	N	[57]
	Plutella xylostella (Diamondback Moth)	endoparasitoid	altered gene expression	reduced methylation	n/a	N	[58]

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Transgenerational effects on pest evolution

Drosophila melanogaster (Fruit Fly)	Heat shock or osmotic stress	n/a	n/a	heterochromatin disruption	Y	[59]

381

382   Figure Legends.

383   Figure 1. Examples of how changes in methylation status of in different gene regions can effect

384   gene expression. Compared to the "normal" unmethylated region, A) has promoter methylation,

385   leading to decreased gene expression; B) exhibits methylation in transposable element regions,

386   leading to those elements not being expressed, and C) shows gene body methylation as found in

387   arthropods, leading to increased gene expression as well as an increased variety of splice variants

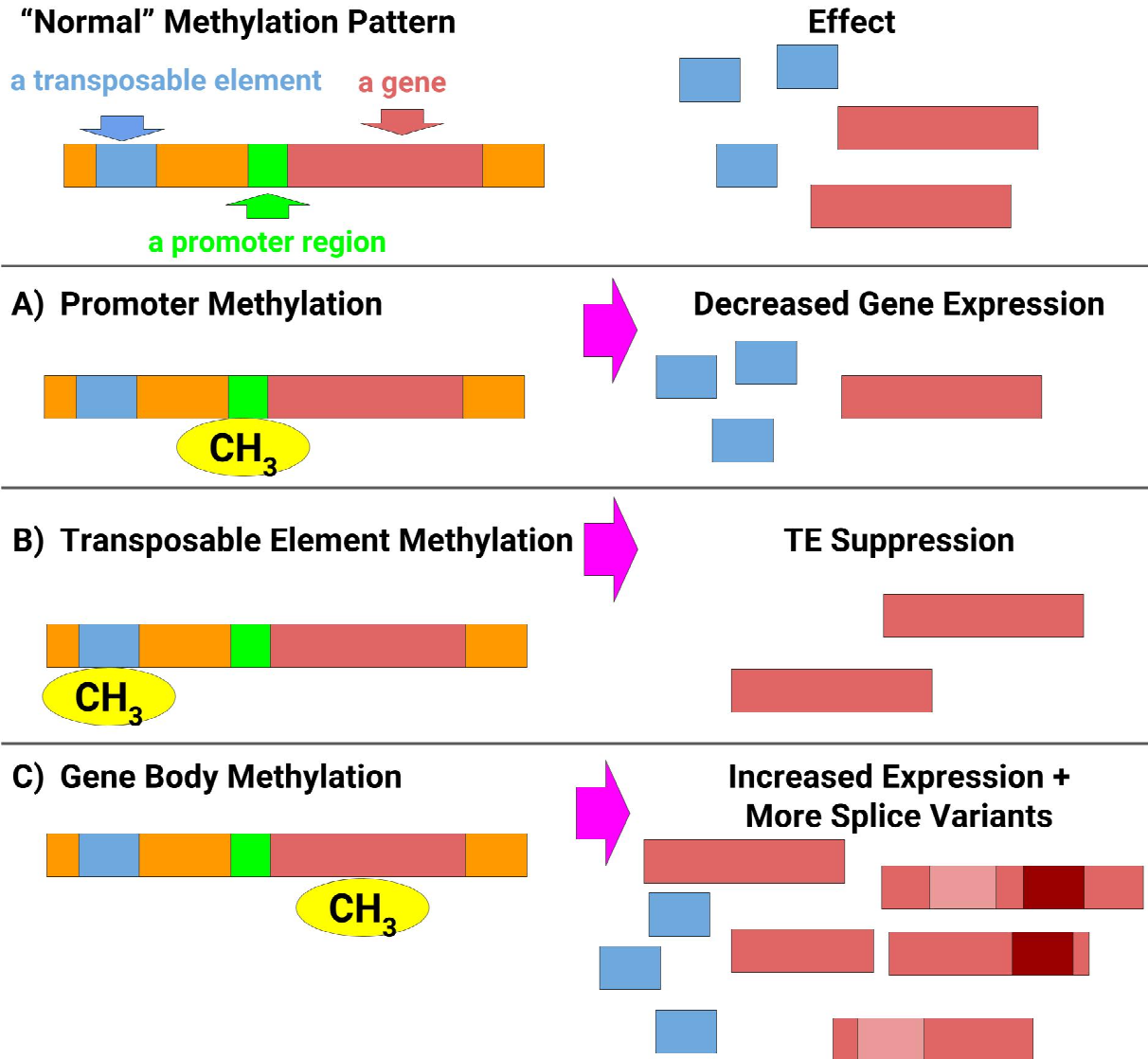388   in those transcripts.

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390   Figure 2. How exposure to a stressor may lead to heritable epigenetic changes that could lead to

391   stress-resistant phenotype in an invasive agricultural insect pests.

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Mechanisms of Methylation and Gene Expression in Insects
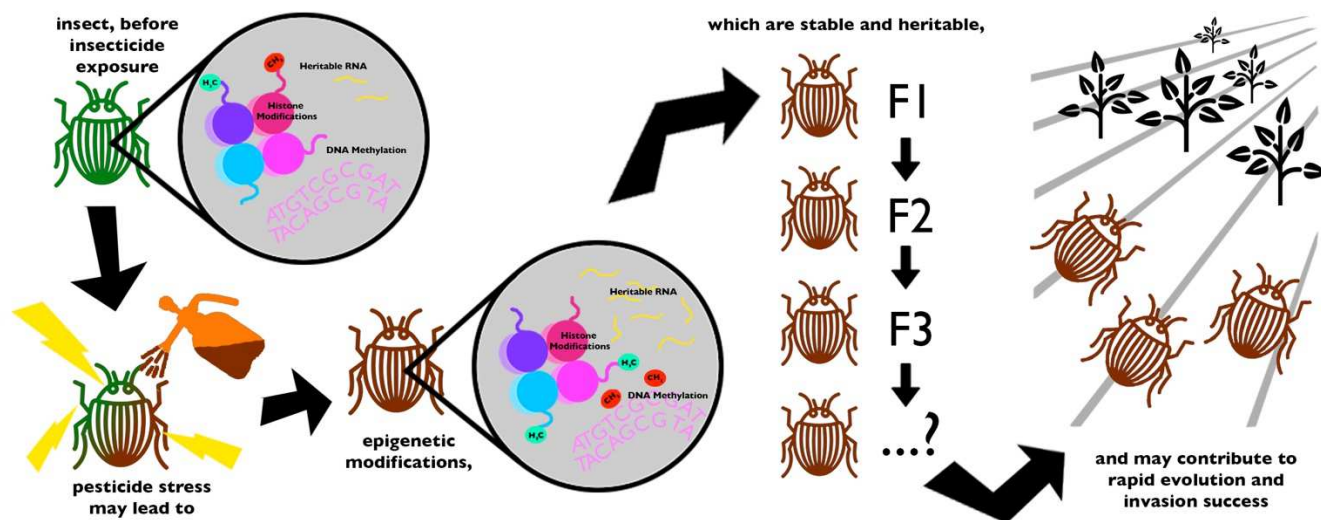

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399   Brevik et al. Figure 1.

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Transgenerational effects on pest evolution

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406   Brevik et al. Figure 2.

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insect, before insecticide exposure

Heritable RNA

H₃C

Histone Modifications

DNA Methylation

ATGTCGCGGAT
TACAGCGCCTA

which are stable and heritable,

F1

F2

F3

....?

pesticide stress may lead to

epigenetic modifications,

Heritable RNA

Histone Modifications

H₃C

DNA Methylation

H₃C

ATGTCGCGGAT
TACAGCGCCTA

and may contribute to rapid evolution and invasion success