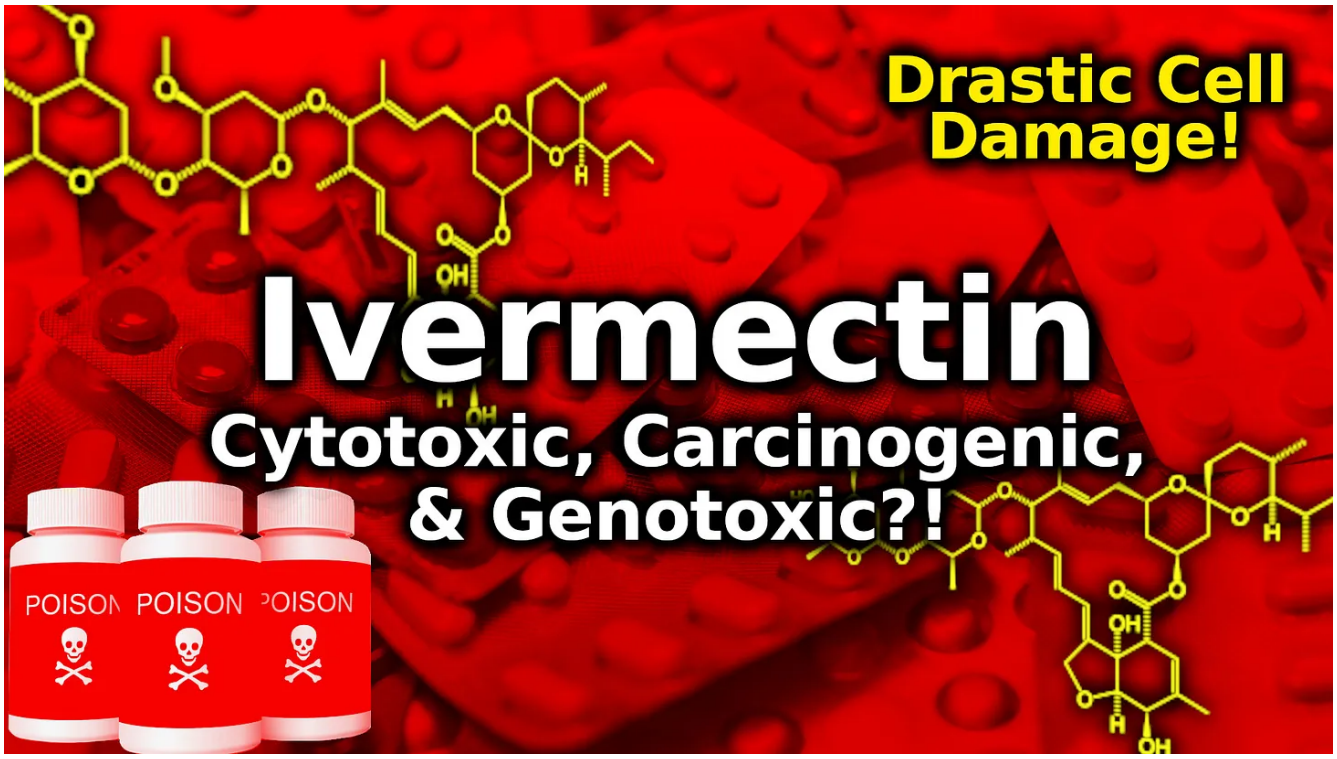
Ivermectin Is Cytotoxic & Genotoxic (Damaging To Cells And DNA) & Possibly Carcinogenic (Cancer Causing)

Why were we told this was safe?

Tim Truth
Jan 3

17 22

Video walkthrough now available here:



Ivermectin Cell & DNA Toxicity Study By Zhang Et Al

In a study called 'Ivermectin Confers Its Cytotoxic Effects by Inducing AMPK/mTOR-mediated Autophagy and DNA2 Damage' Zhang Et Al (full writeup here)

> "Ivermectin has significant ability to induce DNA oxidative damage and enhance autophagy in HeLa cells"

> “The accumulation of IVM in animal tissues and the excretion of urine and feces in the environment is the major source of potential toxicity… Human consumption of meat or milk contaminated with livestock can result in exposure to high levels of IVM exposure.”

> “As expected, we found that IVM can induce oxidative double-stranded damage in HeLa cells, indicating that IVM has potential genotoxicity to human health. In addition, we observed the formation of LC3-B in HeLa cells, the accumulation of Beclin1, the degradation of p62 and the activation of the AMPK/mTOR signal transduction pathway.”

> “We conclude that IVM produces genotoxicity and cytotoxicity by inducing DNA damage and AMPK/mTOR-mediated autophagy, thereby posing a potential risk to human health.”

> “As shown in Fig. 1A, the cell clone formation rate decreased gradually with the increase of IVM concentration after 6 h of drug administration.”

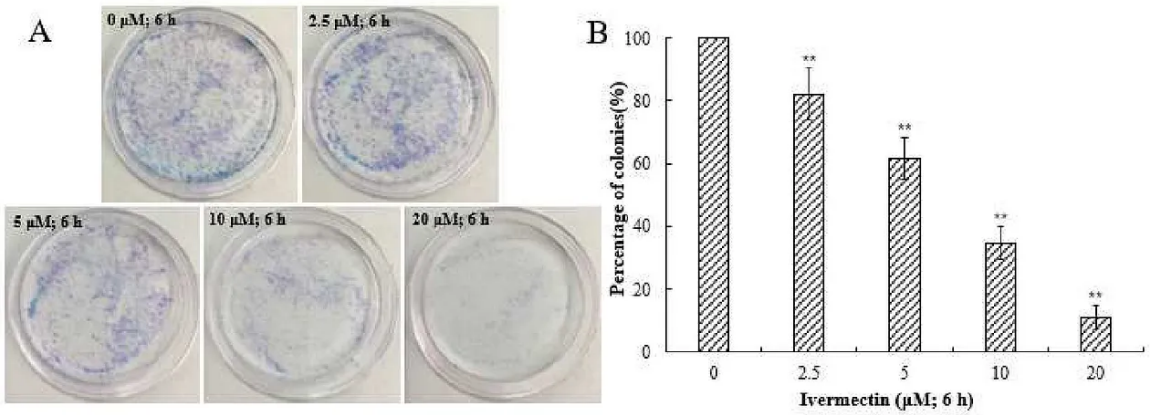


Fig.1. IVM decreases HeLa cells colony formation. (A) After treated with IVM (2.5, 5, 10and 20 μM) for 6 h, colonies were stained with Giemsa. (B) The percentage of colonies were significantly decrease in HeLa cells. The data are shown as the means ± SD of three independent experiments. **p < 0.01.

https://www.sciencedirect.com/science/article/abs/pii/S0045653520316428

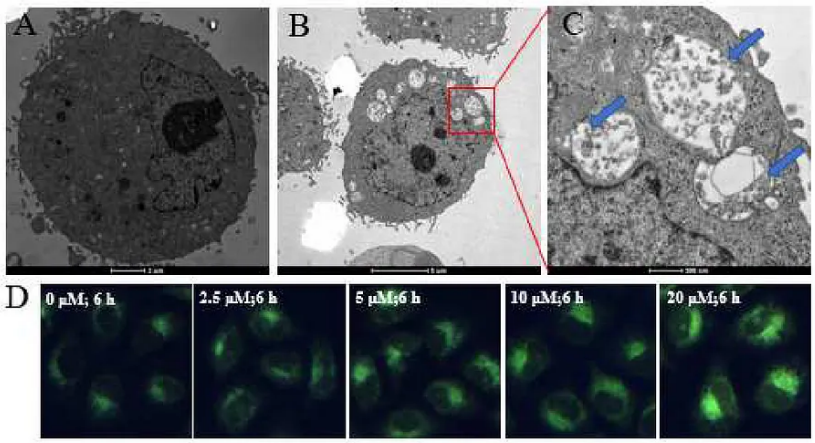


Fig.2. IVM induced autophagy on HeLa cells. (A) After treated with IVM, the images of the HeLa cells were taken by a transmission electron microscope (TEM). (B) (C) Numerous autophagic vacuoles (blue arrows) were observed in spinetoram-treated cells. (D) HeLa cells were treated with IVM for 6 h and stained with MDC.

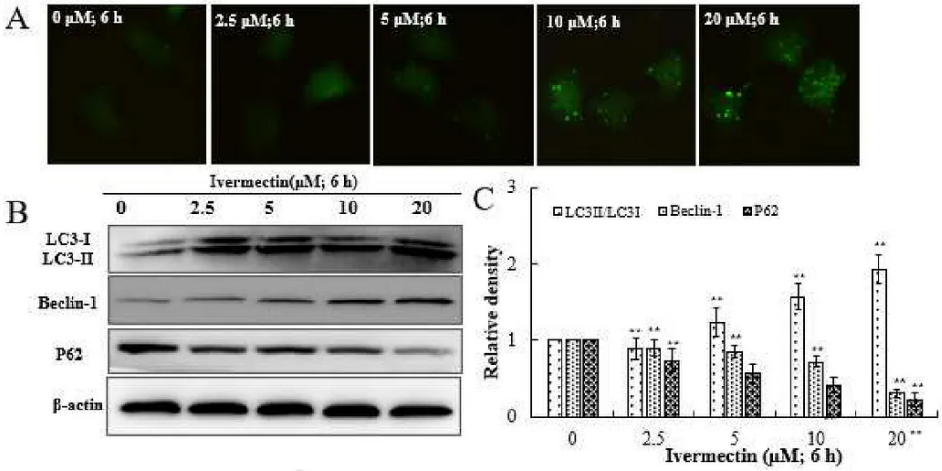


Fig. 3. IVM induced autophagy on HeLa cells. (A) HeLa cells were incubated with Ad-GFP-LC3B and then treated with IVM for 6 h, the autophagosome were analyzed by fluorescence microscopy. (B) After treated with IVM for 6 h, the expression of autophagy-associated proteins LC3, Beclin 1 and P62 in HeLa cells were detected by western blot. (C) Densitometry evaluation of three independent experiments was carried out, each value is the mean ± SD. *$p < 0.05$, **$p < 0.01$. The data shown are the mean from three independent experiments. Each value is the mean ± SD of three determinations.

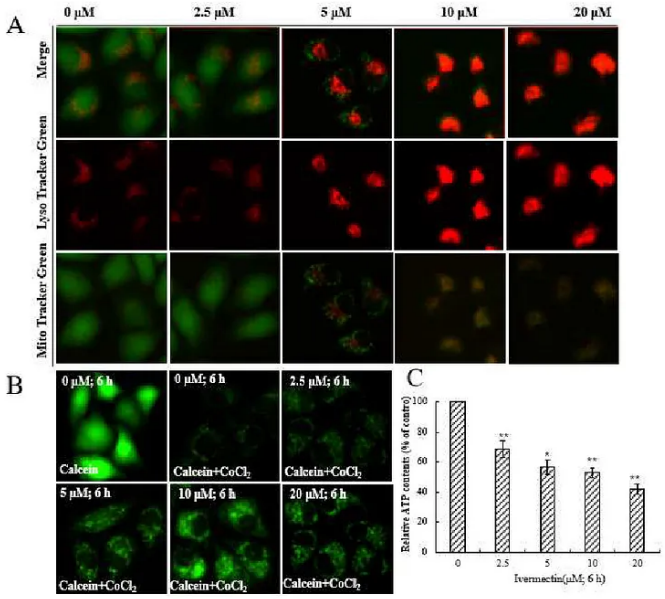


Fig.5. IVM induced mitophagy in HeLa cells. (A) After treated with IVM for 6 h, mitochondria and lysosomes were stained with Mito-Tracker and Lyso Tracker Red, then detected by fluorescence microscopy. (B) After treated with IVM for 6 h, the mPTP opening was detected by co-loading with calcein-AM and $CoCl_2$. (C) After treated with IVM for 6 h, ATP content was measured. All the experiments were performed in triplicates, each value is the mean ± SD. *p < 0.05, **p < 0.01.

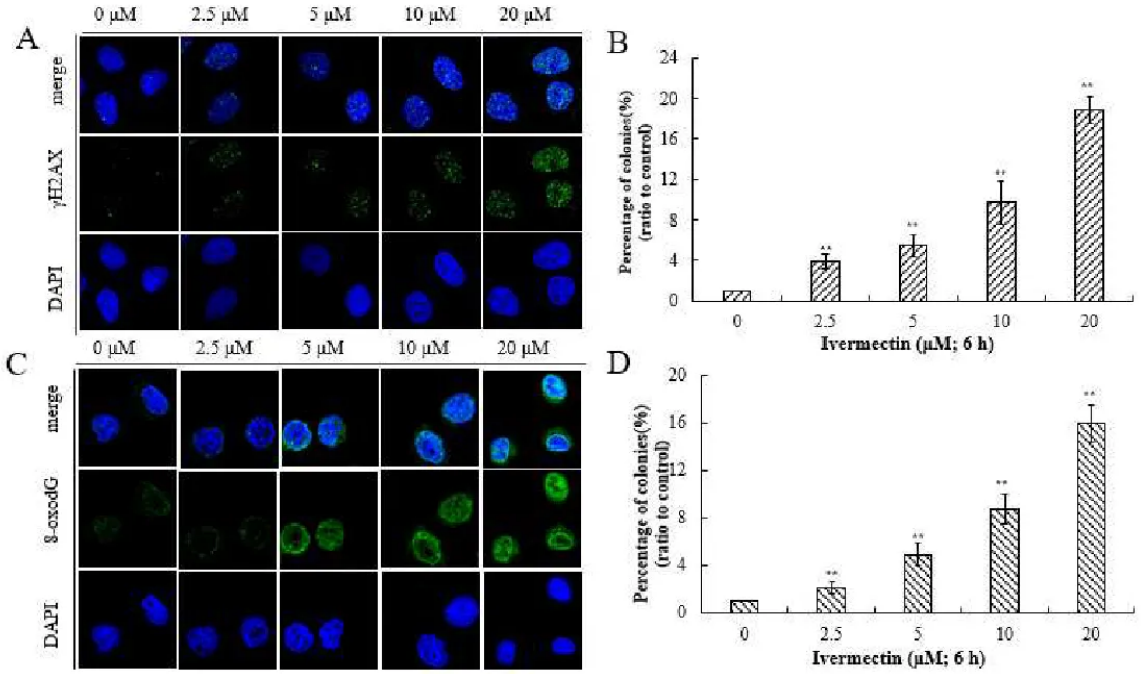


Fig. 7. IVM induced DNA damage in HeLa cells. (A) Anti-γH2AX monoclonal antibody was used to detect DNA damage foci immunofluorescence and DAPI was for nuclei staining. (B) Relative density of γH2AX in the treatment of AVM for 6 h analysis results. (C) Anti-8-oxodG monoclonal antibody was used to detect DNA damage foci immunofluorescence and DAPI was for nuclei staining. (D) Relative density of 8-oxodG in the treatment of AVM for 6 h analysis results. Data was calculated by mean ± SD of three independent experiments. **p < 0.01.

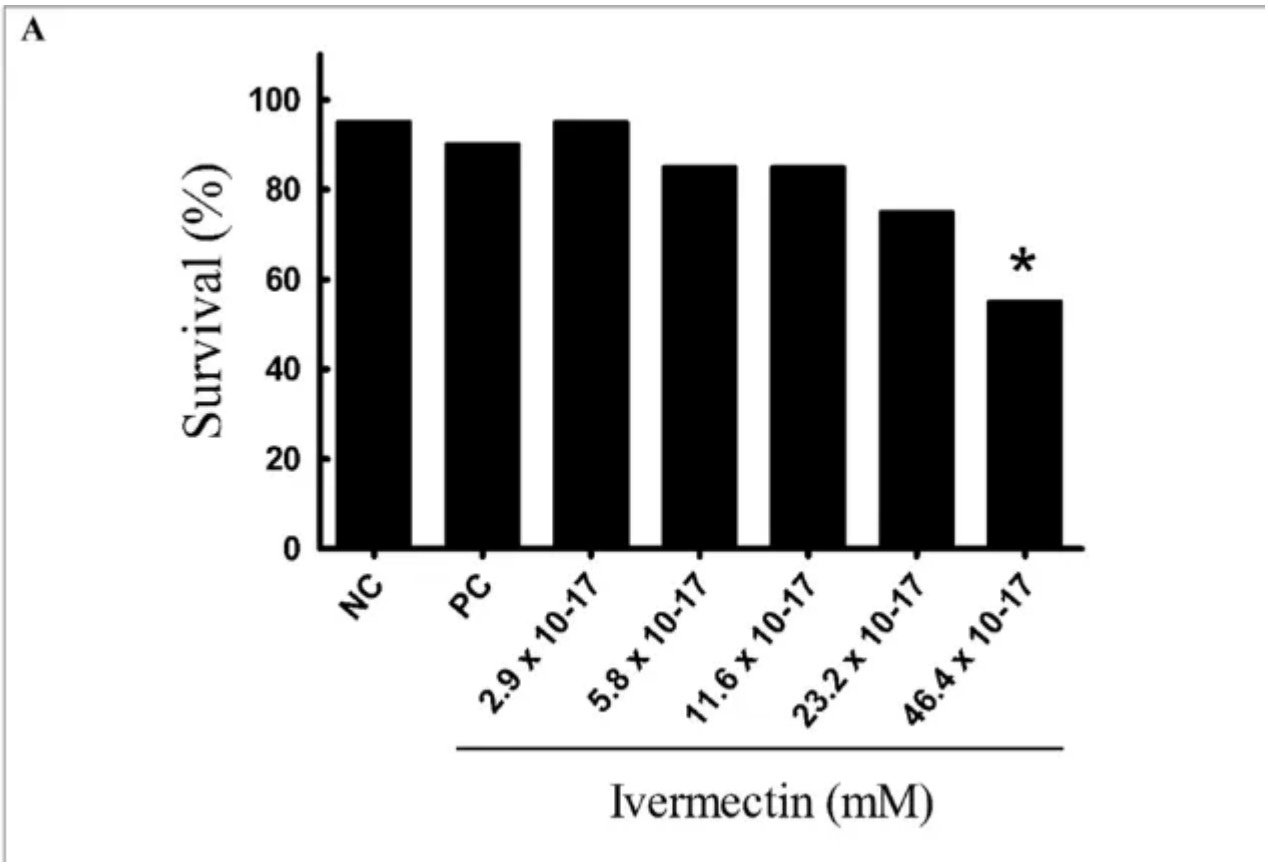
Ivermectin Genotoxicity And Carcinogenicity Observed With Fruit Flies

In a study called 'Genotoxicity and carcinogenicity of ivermectin and amoxicillin in vivo systems' by Aparecida de Sousa et al (full report here),

> "The results revealed that IVM increased the frequency of epithelial tumor in D. melanogaster considering all evaluated concentrations"

> "Findings showed an increase in the frequency of micronuclei in T. pallida treated with 11.42, 22.84 and 45.68 x 10 –5 mM of IVM. We conclude that chronic exposure to IVM is directly associated with events resulting from genetic instability (genotoxicity and carcinogenicity)."

Ivermectin appears to drastically reduce survival rate of fly progenies as the dose is increased:

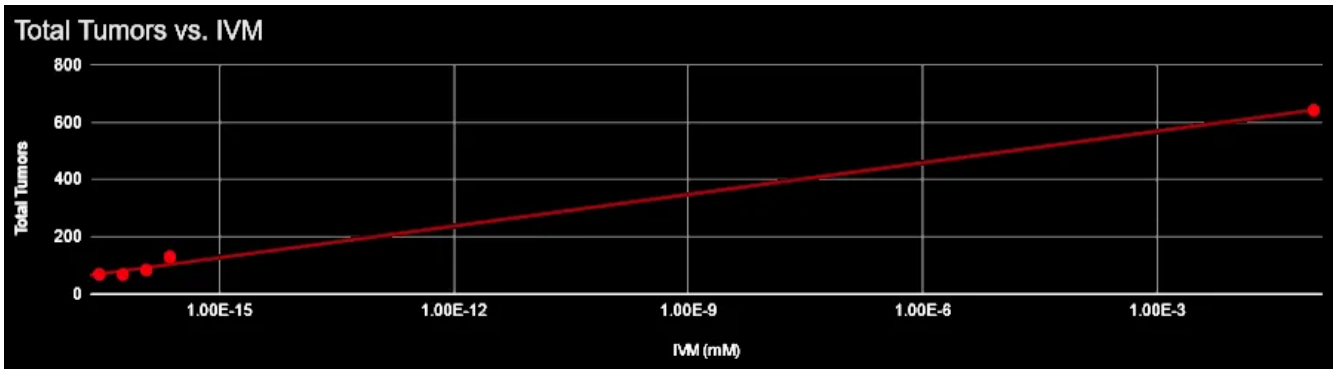


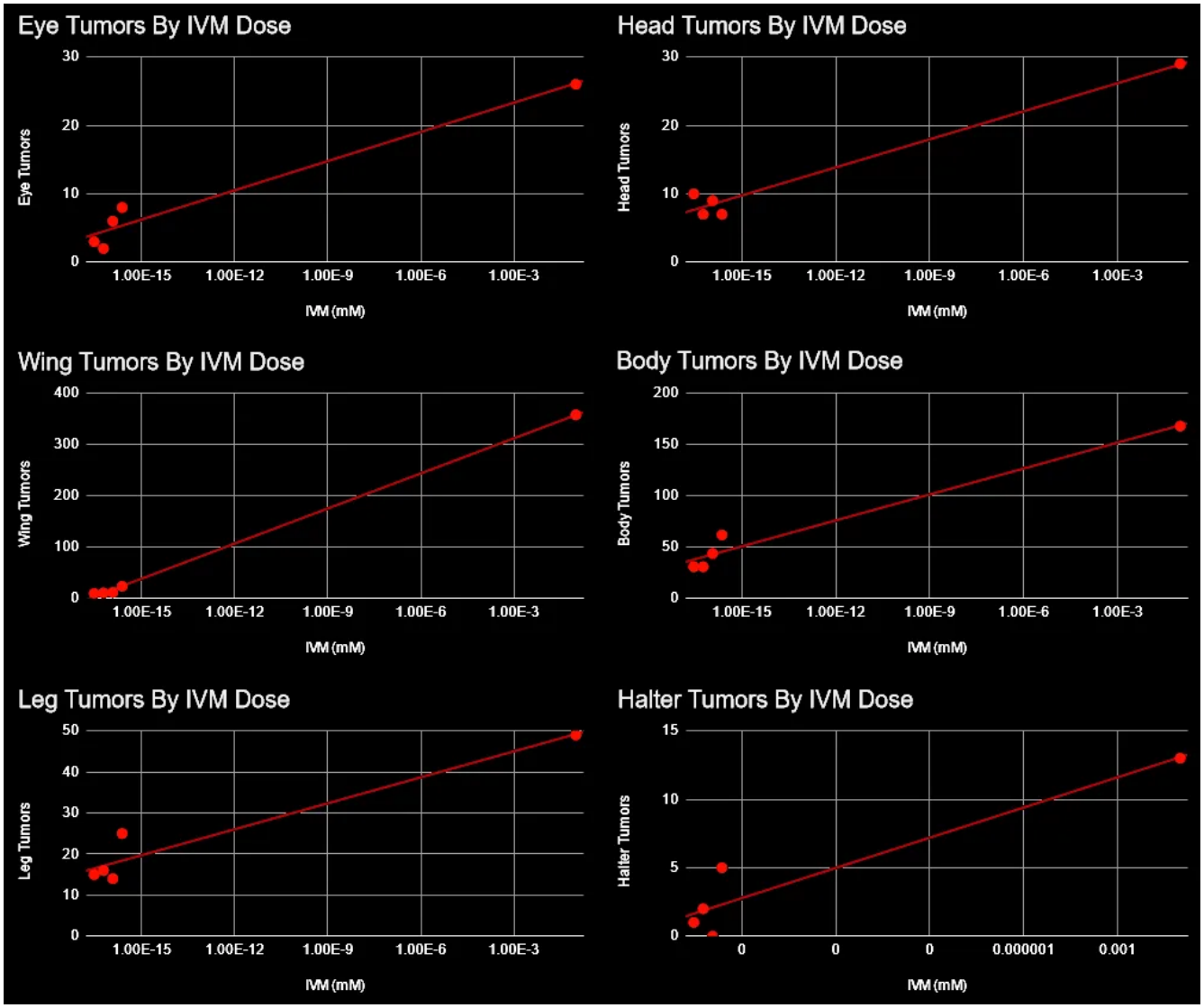
Frequency Of Tumor Clones By IVM Treatment Dosage:

Table 1
Frequency of tumor clones observed in heterozygous to *wts* tumor suppressor gene of *Drosophila melanogater* treated with different concentrations of Ivermectin (IVM), ultrapure water (negative control) and Mitomycin C – MMC (positive control).

Treatment mM		Number of individuals	Number of tumor analyzed (total of tumors)						
			Eyes	Head	Wings	Body	Legs	Halters	Total
Negative control		200	0.005 (01)	0.000 (00)	0.030 (06)	0.150 (30)	0.020 (04)	0.000 (00)	0.205 (41)
MMC	0.1	200	0.130 (26)*	0.145 (29)*	1.790 (358)*	0.840 (168)*	0.245 (49)*	0.065 (13)*	3.215 (643)*
IVM	2.9×10^{-17}	200	0.015 (03)	0.050 (10)*	0.050 (10)	0.155 (31)	0.075 (15)*	0.005 (01)	0.350 (70)*
IVM	5.8×10^{-17}	200	0.010 (02)	0.035 (07)*	0.055 (11)	0.155 (31)	0.080 (16)*	0.010 (02)	0.345 (69)*
IVM	11.6×10^{-17}	200	0.030 (06)	0.045 (09)*	0.060 (12)*	0.220 (44)	0.070 (14)*	0.000 (00)	0.425 (85)*
IVM	23.2×10^{-17}	200	0.040 (08)	0.035 (07)*	0.120 (24)*	0.310 (62)*	0.125 (25)*	0.025 (05)*	0.655 (131)*

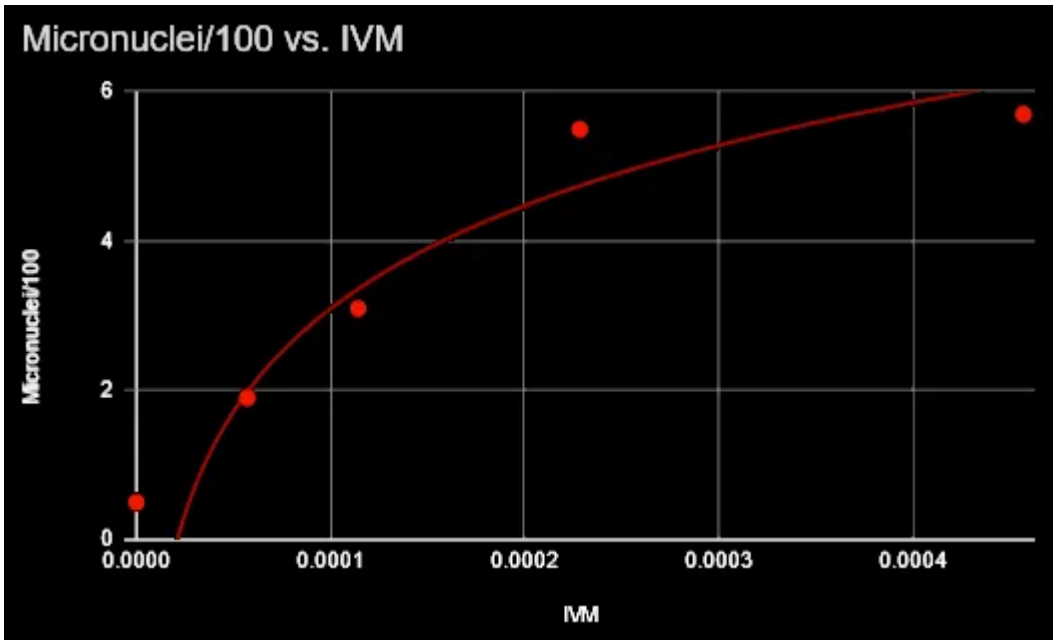
Statistical diagnoses according to the Mann-Whitney test. Significance level ($p \leq 0.05$).
IVM: Ivermectin; MMC: Mitomycin C (positive control). Negative control: ultrapure water.





> "It was observed a dose-dependence in the frequency of MN in T. pallida considering the highest concentrations (11.42, 22.84 and 45.68 × 10−5 mM) differing statistically ($p \leq 0.05$) from the negative control, evidencing a genotoxic effect of IVM"

> "The results observed in D. melanogaster and T. pallida showed that IVM can increase the damage in the genetic material, leading to genetic instability."



Why fruit flies? The authors explain:

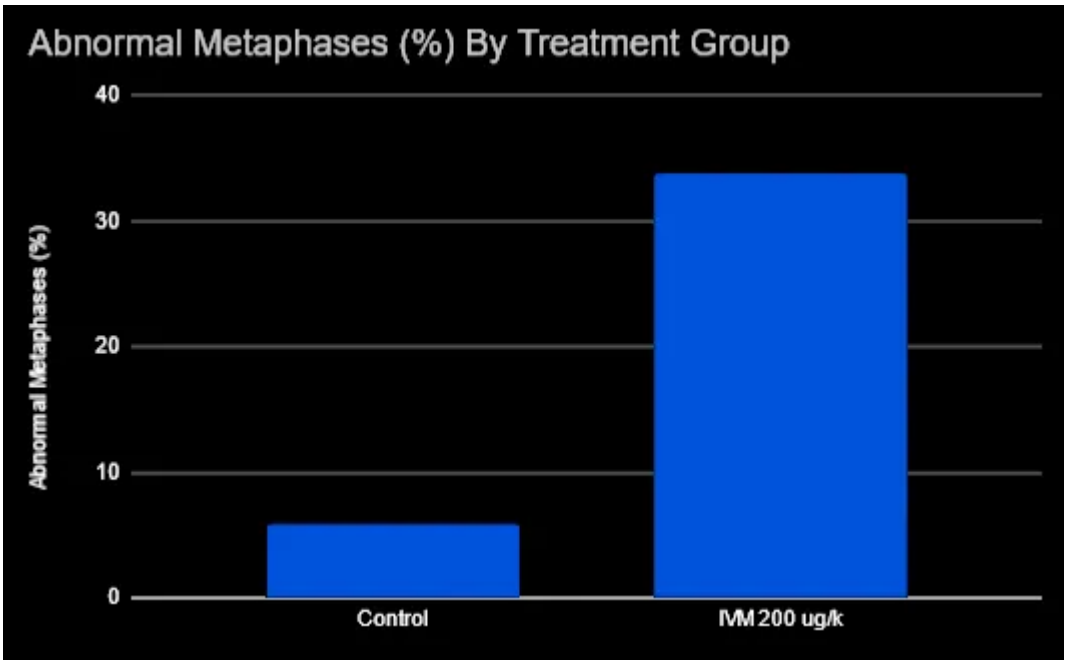
> "In D. melanogaster, the test for the detection of epithelial tumor (ETT) represents one of the most promising alternatives to evaluate and identify possible carcinogens (Nepomuceno, 2015) … This test has also been used to verify carcinogenic events of different substances (Orsolin et al., 2012; Morais et al., 2018; Naves et al., 2018)."

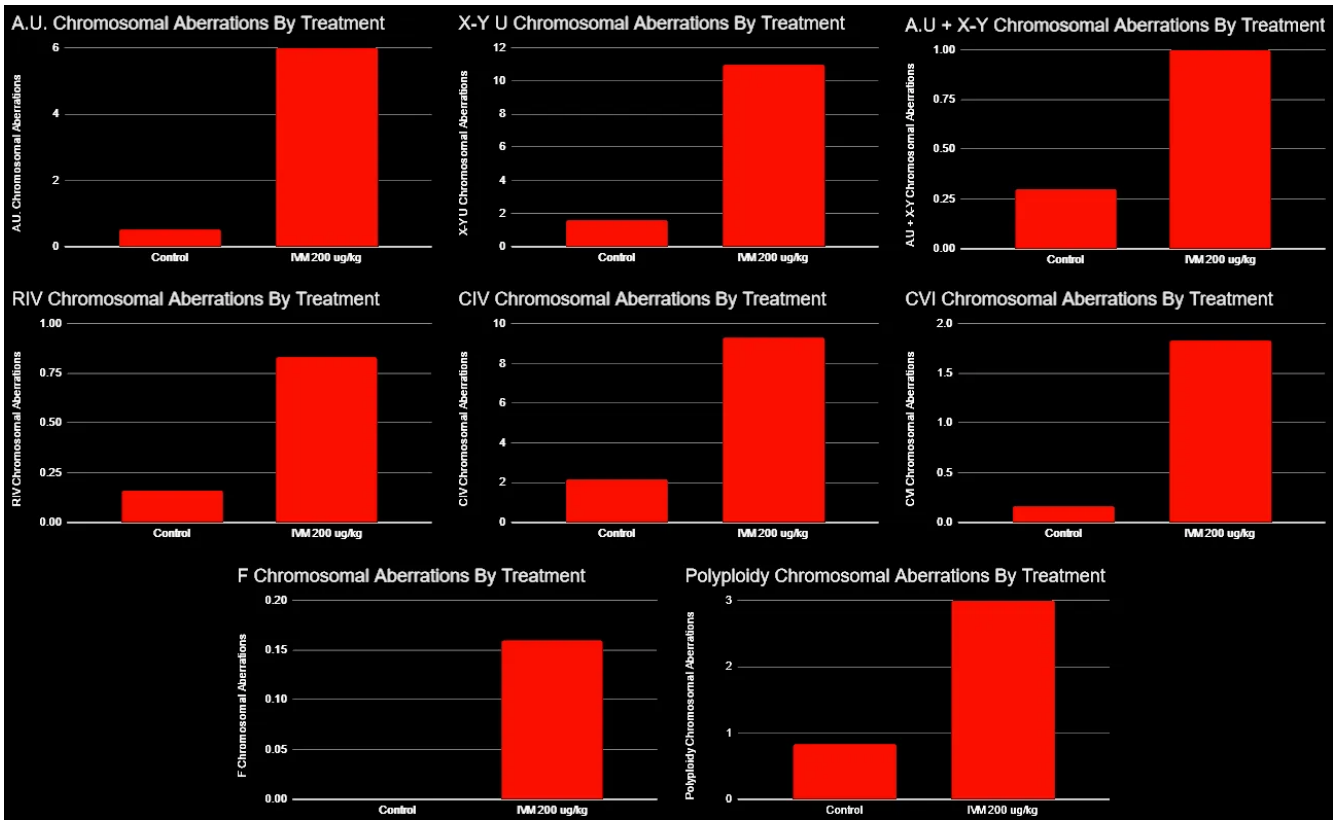
Ivermectin Mutagenicity In Swiss Albino Mice

In a study titled 'The mutagenic effects of ivermectin in germinal cells and serum protein of the mouse' by Sweify et al

> "Ivermectin… is extremely toxic to fish and aquatic life. Some animals showed reduction in the fertility, the number of variable fetuses and sperm count following treatment with (IVM)."

> "Analysis of the treated samples revealed significant increase in meiotic aberrations, 33.83% vs 5.8% for the control ($P < 0.001$)… These findings supports the mutagenicity of IVM"





> "Effects of ivermectin on spermatocyte chromosomes: … spermatocytes of the treated samples revealed significant increase in chromosome aberrations over the control values"

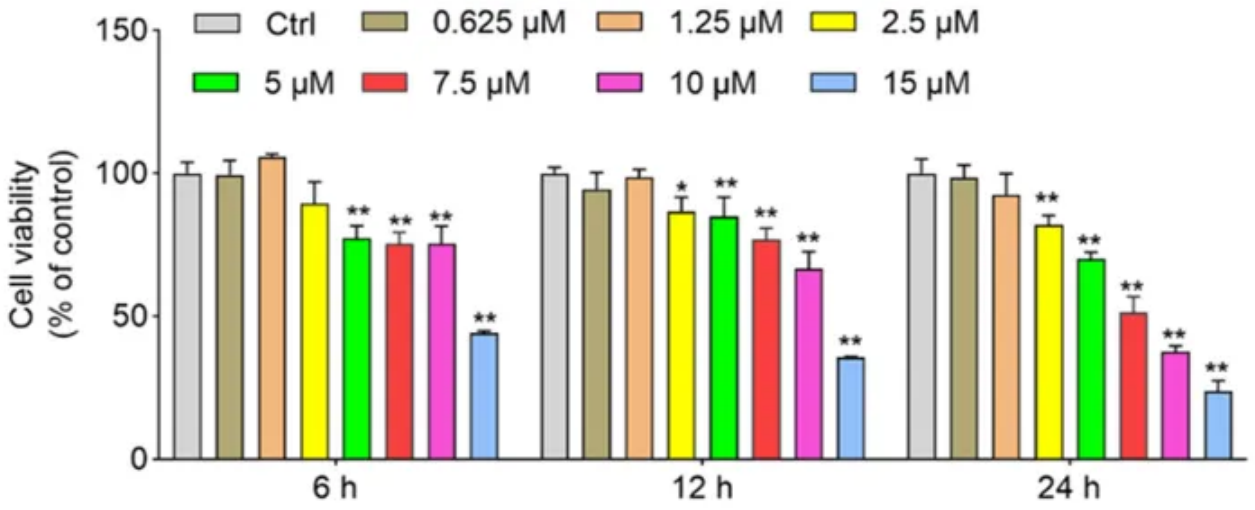
> “The present observations pointed to the mutagenic effects of IVM. The frequency of translocation is significantly higher than that found in the control samples”

Ivermectin Vs Human Neuroblastoma SH-SY5Y Study

In a study called ‘Ivermectin-Induced Apoptotic Cell Death in Human SH-SY5Y Cells Involves the Activation of Oxidative Stress and Mitochondrial Pathway and Akt/mTOR-Pathway-Mediated Autophagy’ by Zhange et al

> “The results show that IVM treatment (2.5–15 μM) for 24 h could induce dose-dependent cell death in SH-SY5Y cells. Compared to the control, IVM treatment significantly promoted the production of ROS, mitochondrial dysfunction, and cell apoptosis. IVM treatment also promoted mitophagy and autophagy, which were charactered by the decreased expression of phosphorylation (p)-Akt and p-mTOR proteins, increased expression of LC3II, Beclin1, ATG5, PINK, and Pakin1 proteins and autophagosome formation… our results reveal that IVM could induce autophagy and apoptotic cell death in SH-SY5Y cells”

> “IVM-induced cytotoxicity is dose- and time-dependent. At 6 h and 12 h, IVM treatment at 15 μM significantly decreased the cell viabilities to 44.3% and 35.6% (both $p < 0.01$), respectively; at 24 h, IVM treatment at 0.625, 1.25, 2.5, 5, 7.5, 10, and 15 μM decreased the cell activities to 98.5%, 92.4%, 81.9% ($p < 0.01$), 70.2% ($p < 0.01$), 51.3% ($p < 0.01$), 37.6% ($p < 0.01$), and 23.8% ($p < 0.01$) (Figure 1), respectively. Correspondingly, marked cell morphology changes, including a spindle-like cell body, shrinkage, and dendrite fragmentation in high concentrations of IVM (at 7.5, 10, and 15 μM for 24 h, respectively) were also detected”



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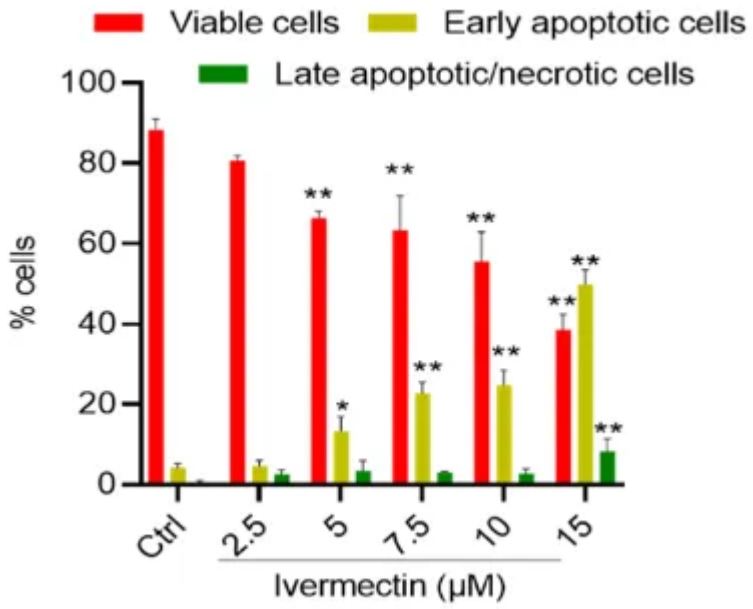

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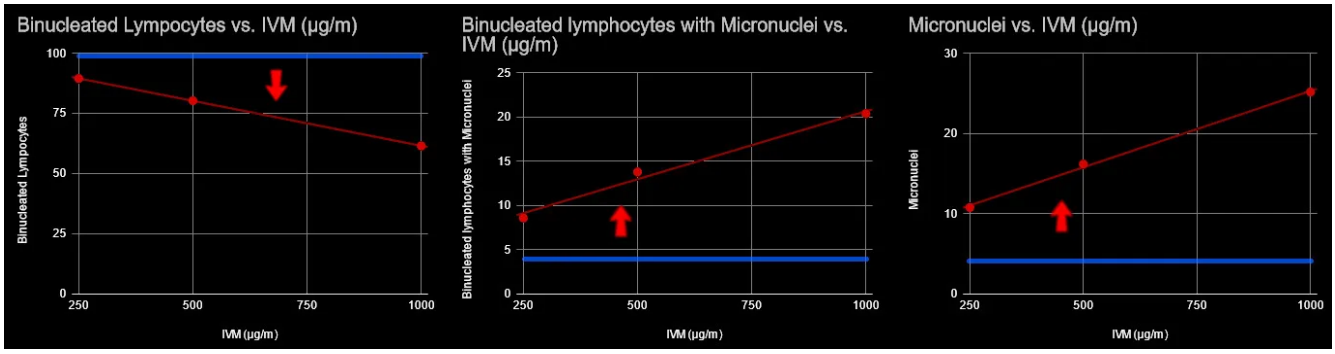
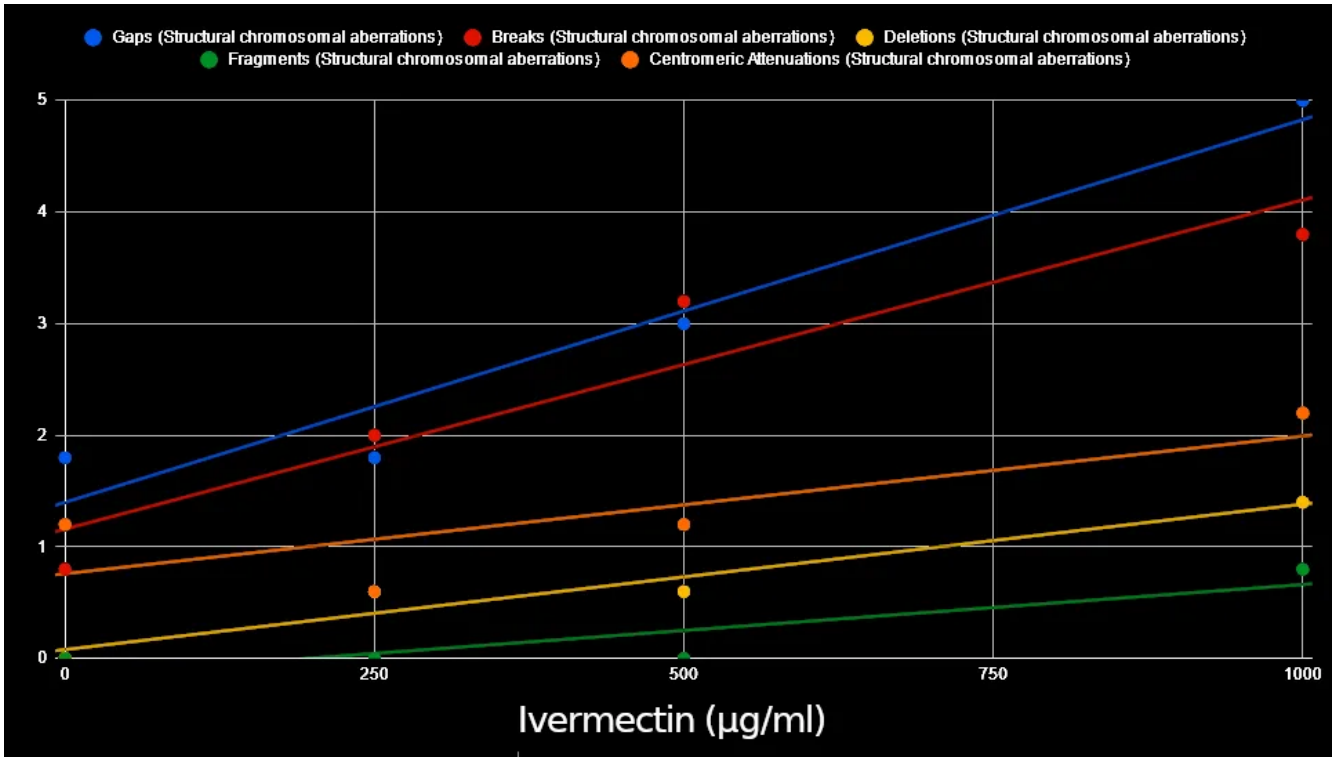
Ivermectin Vs Buffalo Peripheral Lymphocyte Cells

In a paper called 'Antimutagenic Activity of Some Natural supplements on Ivermectin genotoxicity in Lymphocytes of Buffalo' by El-makawy et al,

Cell Abnormalities



Structural Chromosomal Aberrations Observed:



> "Ivermectin induced dose dependent significantly increase in the number of binucleated lymphocytes with micronuclei and also the frequencies of total chromosomal aberrations"

> "In addition, the numbers of binucleated lymphocytes showed dose dependent decrease than control. These results revealed that the drug has a cytotoxic effect on the number of cell divisions. As the micronuclei are small chromatin-containing bodies arising from chromosome fragmentation by breaks or deletion, the results of

> MN formation confirmed our results of chromosomal aberrations indicating the clastogenic effects of ivermectin."

In Vivo Ivermectin Vs Mice Bone Marrow Study

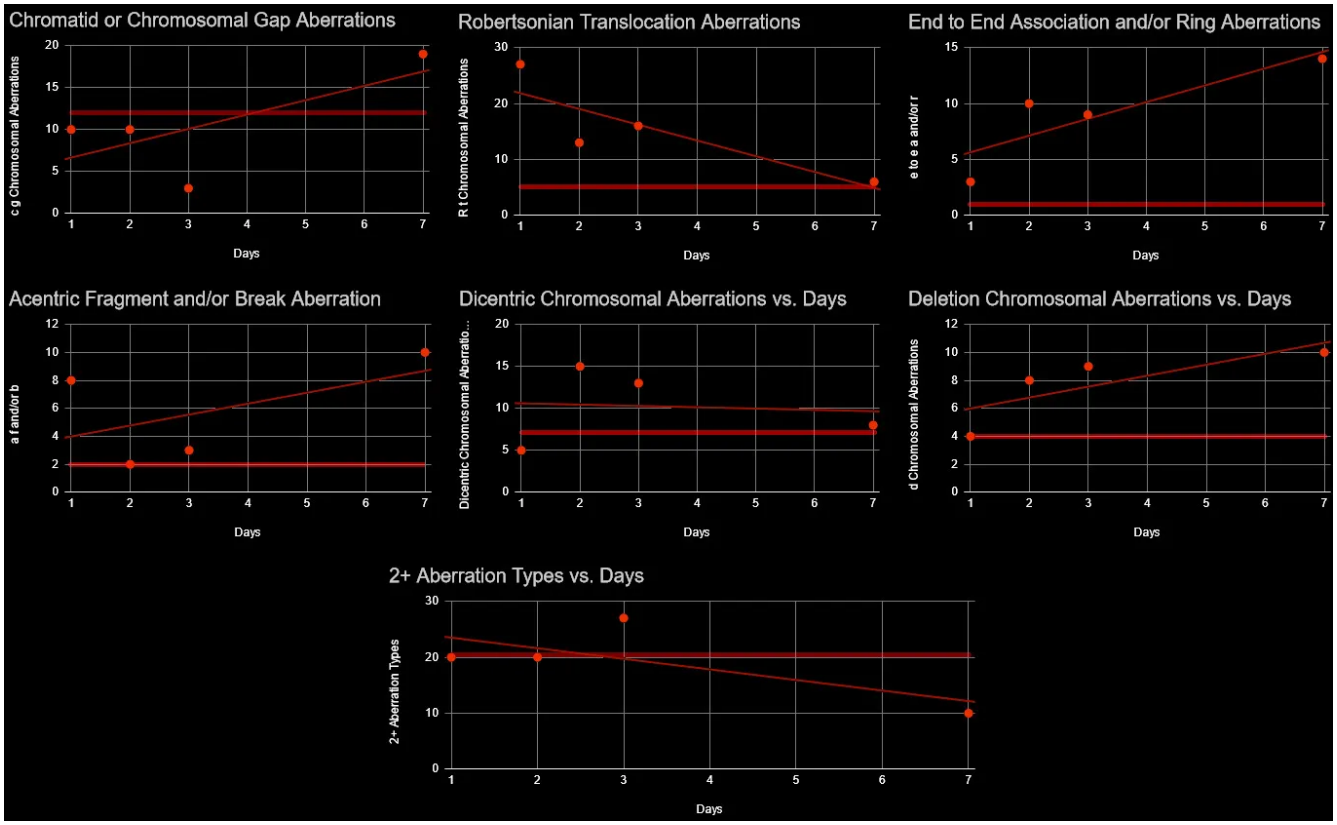
In a study called 'The cytogenetic potential of ivermectin on bone marrow cells of mice in vivo' from Sweify et al:

> "IVM induced high level of chromosome aberrations in somatic cells, as it is ascertained by chromosome aberration assay and micronuclei production in bone marrow cells. This study revealed high clastogenic and genotoxic potential of IVM on mice"

Experiment 1: Single Injection Of Ivermectin

"The Table contains also the different types of chromosomal aberrations recorded in the examined cells. A single i.p. injection of ivermectin resulted in a significant ($P \leq 0.001$) increase in percentage of aberrant cells"

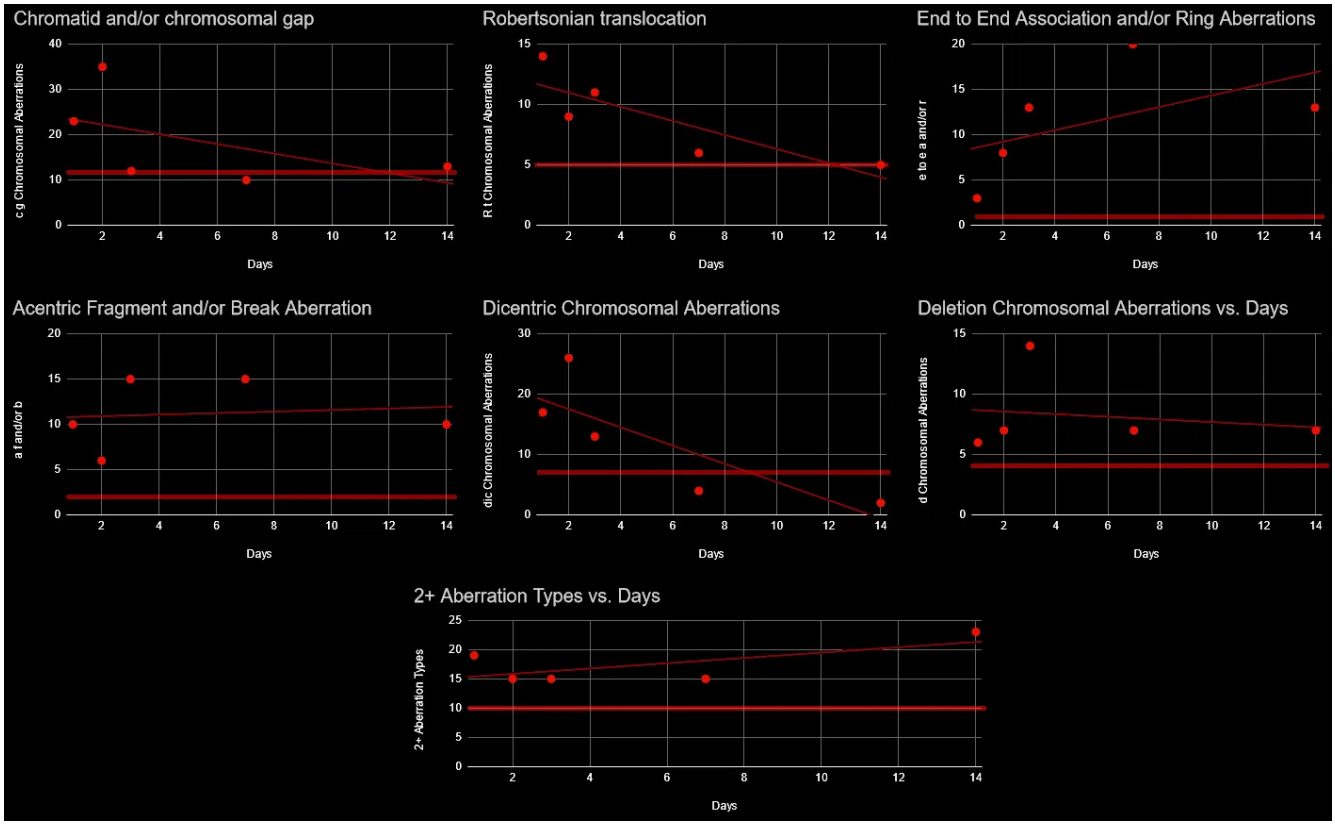
Here are the different chromosomal aberrations that were tracked after the invermectin injection. The transparent horizontal lines are the control levels:



Experiment 2: Two Injections Of Ivermectin

"It is clear from the Table (II) that injection with ivermectin induced high significant increase in the frequency of the damaged cells allover the examined periods (P≤0.001)."

Here are the different chromosomal aberrations that were tracked after the second invermectin injection. The transparent horizontal lines are the control levels:



Study of Genotoxic and Cytotoxic Effects Of Ivermectin In Chinese Hamster Ovary Cells In Vitro

In a study called 'In vitro genotoxic and cytotoxic effects of ivermectin… on Chinese hamster ovary (CHO K1) cells' by Molinari et all, they found that Ivermectin caused DNA-strand breaks in Chinese hamster ovary (CHO(KI)) cells. (Full article)

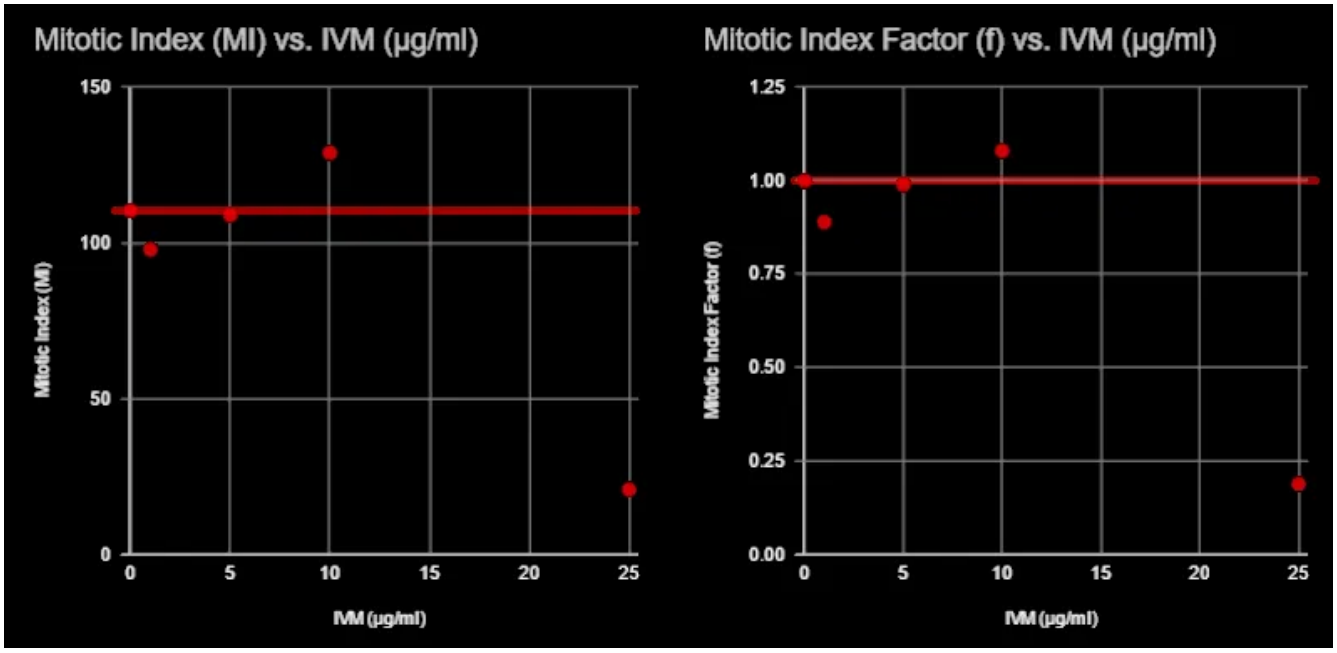
Table 1
Proliferative rate index (PRI), mitotic index (MI) and mitotic index factor (*f*) in control and ivermectin-treated CHO_{K1} cells after 24 h of treatment.

Dose (μg/ml)	Ivermectin		
	PRI[a]	MI[a]	*f*[a]
0.0	1.95 ± 0.02	110.50 ± 0.50	1.00 ± 0.00
BLM[b]	1.60 ± 0.02**	35.00 ± 0.00***	0.35 ± 0.30***
1.0	1.94 ± 0.03	98.00 ± 2.00	0.89 ± 0.07
5.0	1.96 ± 0.00	109.00 ± 3.00	0.99 ± 0,16
10.0	1.95 ± 0.02	129.00 ± 8.00	1.08 ± 0.26
25.0	1.05 ± 0.05***	21.00 ± 9.00***	0.19 ± 0.09***
50.0	ND	ND	ND
100.0	ND	ND	ND
250.0	ND	ND	ND

ND, not determined since a complete cellular death was achieved in cultures.

[a] Results are presented as mean values of pooled data from three independent experiments ± S.E. of the mean.
[b] Bleomycin (BLM, 1.0 μg/ml) was used as positive control.
** $P < 0.01$.
*** $P < 0.001$

Here's a chart of mitotic index (MI) and mitotic index factor (*f*) for each of the lesser doses before the "**complete cellular death**" seen in doses 50μm/ml. The transparent horizontal lines are the control group baseline

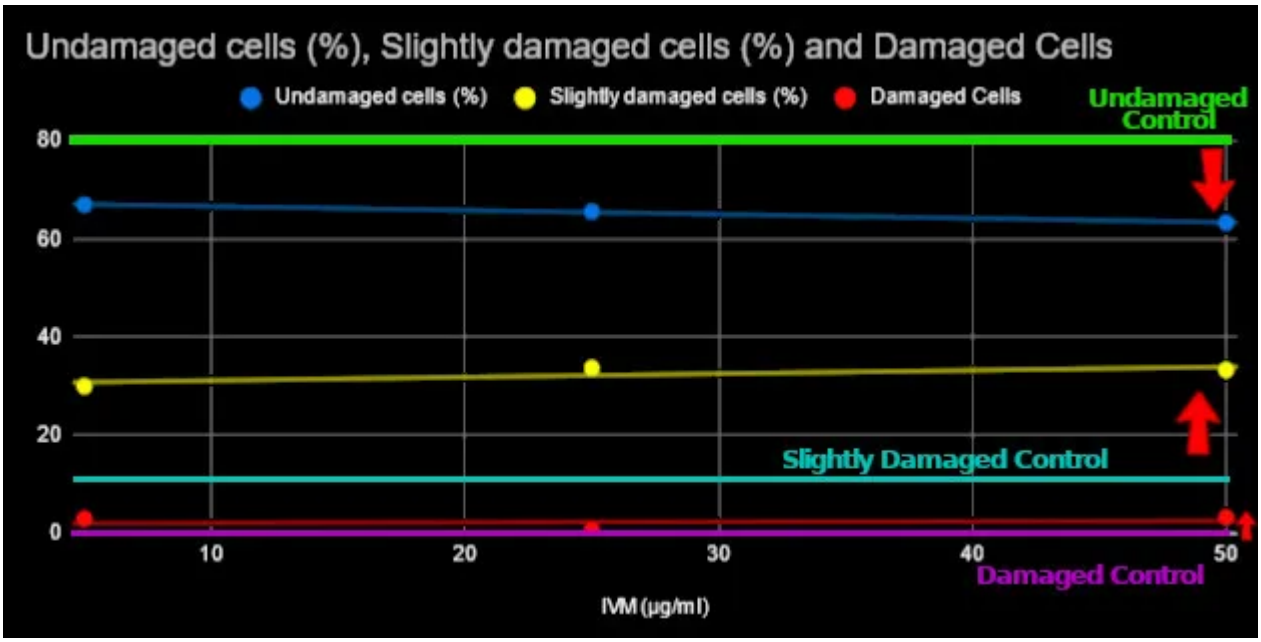


Decrease in mitotic index typically indicates genotoxicity. (Sweify, 2019)

> “IVM exerted a cytotoxic effect of CHO cells within the 25.0–250.0 g/ml concentration-range”

> “Highest [IVM] concentrations (50.0–250.0 g/ml) resulted in cellular cytotoxicity clearly revealed by delaying the cell-cycle progression, decreasing the mitotic activity, and inhibiting cell-growth. It is worth mentioning that both chemicals induced DNA-strand breaks revealed by the comet assay”

> “A brief 80 min pulse-treatment of 5.0–50.0 g/ml of IVM or 25.0 and 50.0 g/ml of ivomec® , resulted in a manifest level of single DNA-strand break induction.”



O’Conner Ivermectin Rat Carcinogenicity Study

In an article called ‘Increased Pathology Incidence in the Forestomach of Rats Maintained on a Diet Containing Ivermectin and Given a Single Dose of N-Methyl-N1-Nitro-N-Nitrosoguanidine’ by O’Conner et al, they observed additional cancers in mice with a small amount (2 ppm) of ivermectin in their diet given a dose of a carcinogen called N-Methyl-N1-Nitro-N-Nitrosoguanidinecalled N-Methyl-N1-Nitro-N-Nitrosoguanidine. From the abstract:

> “No tumors or pathological lesions were observed in the forestomach of the control animals or those given ivermectin alone. However, compared to animals receiving

> MNNG alone, rats maintained on a diet containing ivermectin (2 ppm) and given MNNG… showed an increased number of neoplasms (9/26 vs 3/18; p = 0.30) and a statistically significant fourfold increase in the number of pathological lesions (18/26 vs 3/18; p = 0.002), which include preneoplasia in the forestomach. In all cases, the pathological lesions were more severe in the animals receiving ivermectin and MNNG, compared to those receiving MNNG alone."

Study of Genotoxic and Cytotoxic Effects Of Ivermectin In Mosquito Cells In Vivo

In a study called 'Genotoxic and cytotoxic in vitro evaluation of ivermectin… on Aedes albopictus larvae (CCL-126™) cells' (Full paper):

"IVM… induced DNA-strand breaks enhancing both slightly damaged and damaged cells at 25–50 µg/ml IVM"

"Cytotoxicity was observed at concentrations higher than 25 µg/ml IVM… [Ivermectin] exerted a delay in CCP and a reduction in PRI when 25.0 g/ml was employed whereas cytotoxicity was observed at higher concentration than 50.0 g/ml."

"A marked reduction of about 98% … of MI [mitotic index] compared to controls was noted with 25 µg/ml of IVM"

"NR and MTT assays revealed that [IVM] induced a cell growth inhibition within the 1–250 µg/ml concentration range"

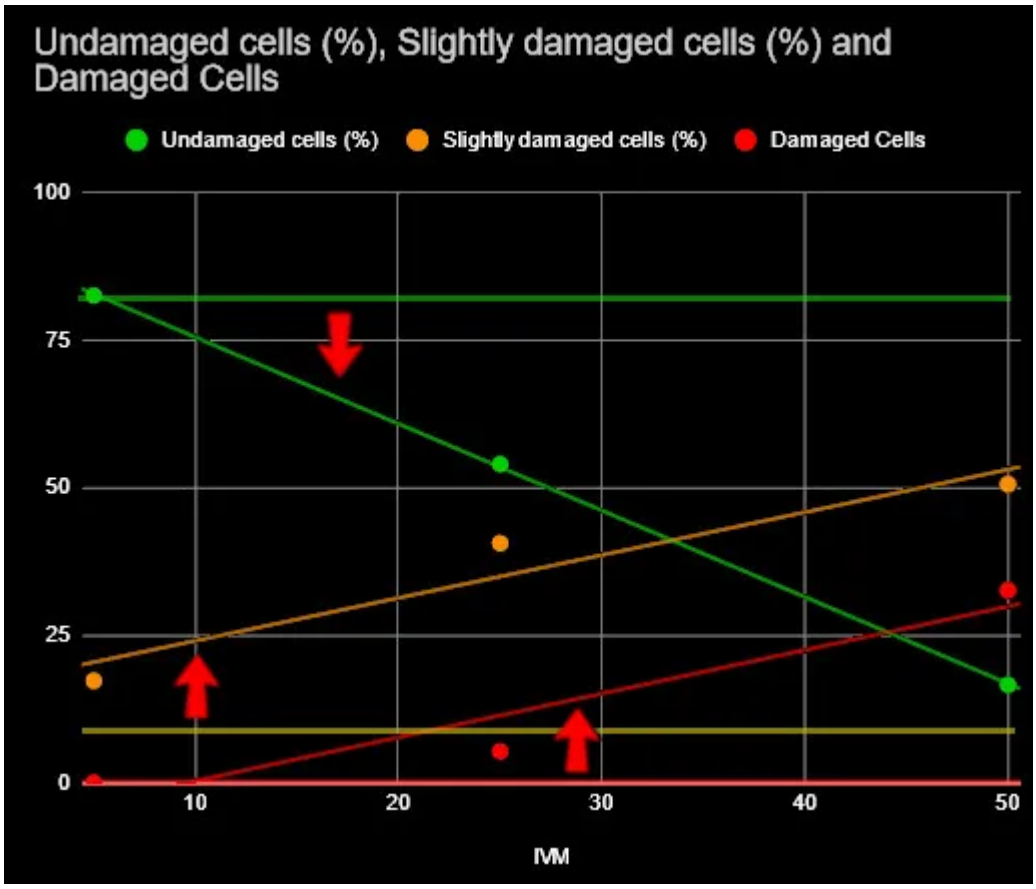
"Data indicated that IVM exerts both genotoxicity and cytotoxicity in insect cells [A. albopictus larvae CCL-126 cells] in vitro"

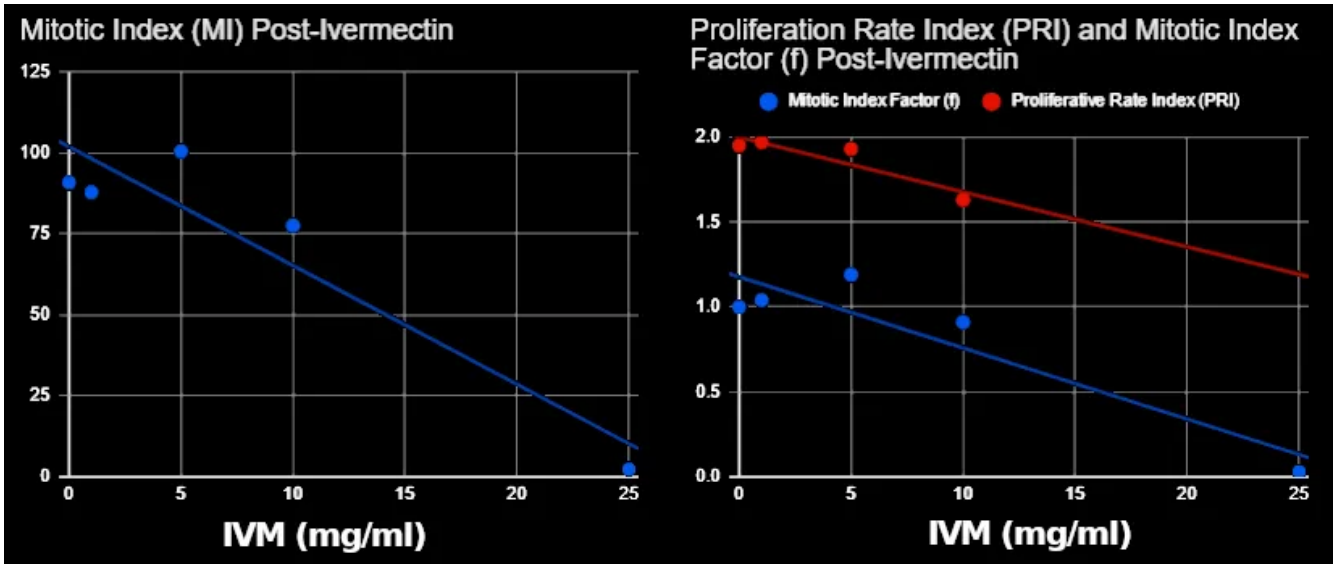
This chart shows the percentage of undamaged, slightly damaged & damaged cells with the addition of Ivermectin (measured in µg/ml). The transparent horizontal lines are the control levels.

PRI, MI, and MI factor (f) in control and IVM-treated *A. albopictus* cells after 24 h of treatment.

Concentration ($\mu g\,mL^{-1}$)	IVM		
	PRI[a]	MI[a]	f[a]
0.0	1.95 ± 0.03	91.00 ± 9.00	1.00 ± 0.00
BLM[b]	1.64 ± 0.18*	89.67 ± 8.88	1.03 ± 0.11
1.0	1.97 ± 0.02	88.00 ± 5.57	1.04 ± 0.21
5.0	1.93 ± 0.01	100.67 ± 5.21	1.19 ± 0.22
10.0	1.63 ± 0.15*	77.66 ± 5.70	0.91 ± 0.17
25.0	ND	2.33 ± 1.45***	0.03 ± 0.01
50.0	TOX	TOX	TOX
100.0	TOX	TOX	TOX
250.0	TOX	TOX	TOX

Notes: ND – not determined (insufficient M_2); TOX– toxic.
[a]Results are presented as mean values ± S.E. of three independent experiments.
[b]Bleomycin (BLM, 1.0 $\mu g\,mL^{-1}$) was used as positive control.
*$p < 0.05$ and ***$p < 0.001$.





Decrease in mitotic index typically indicates genotoxicity. (Sweify, 2019)

Why insect cells? The authors' address this:

> "It was demonstrated that among insects, mosquito cells cultures provide a useful in vitro system for studying deleterious effects induced by xenobiotics (Mukherjee et al.

> 1986; Bolza ń et al. 1998, 2000). Investigations demonstrated that DNA damage induced by different chemicals was found to be less extensive and repaired more efficiently in Aedes albopictus larvae cell lines compared to Chinese hamster ovary (CHO-K1) cells”

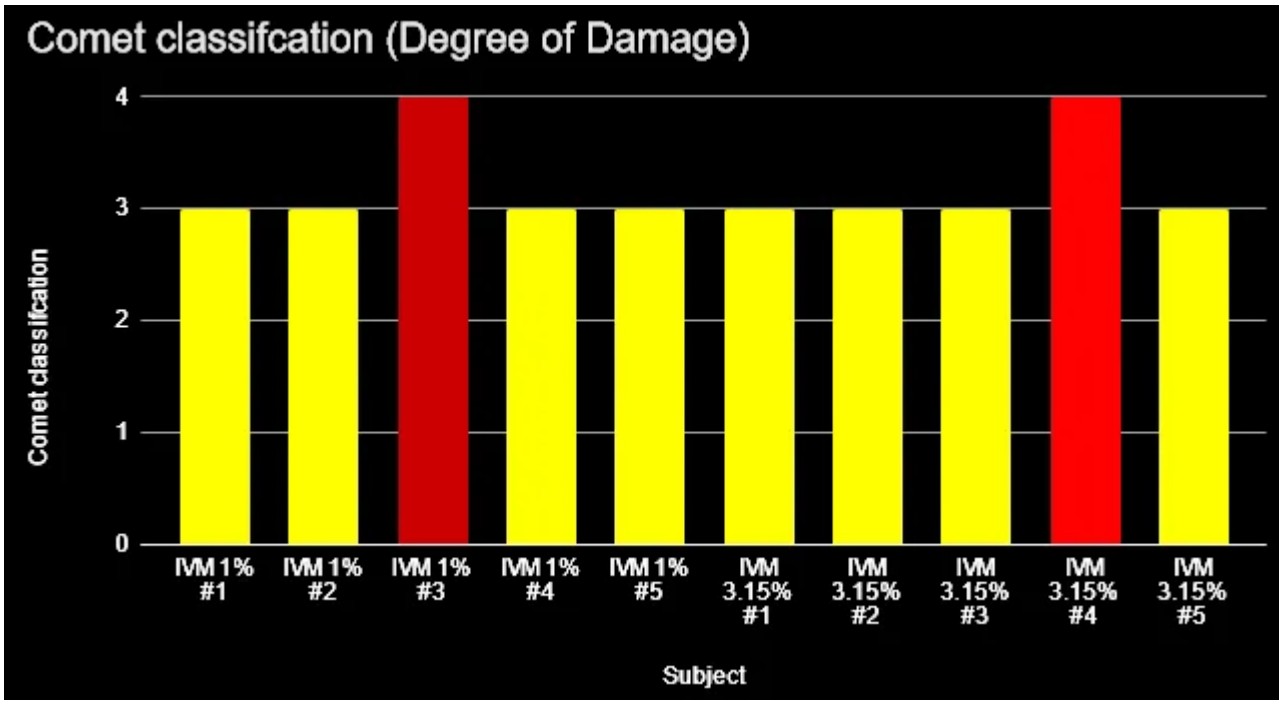
Ivermectin In Cebu Brahman Cows

In a paper called ‘Comet assay to determine genetic damage by the use of ivermectin in zebu cows’

> “The values of classification of comets indicate cells with high levels of damage (grade 3: cells with high damage). The rate of DNA damage of the treatment to 1% to 3.15% was significant… The results obtained in this study demonstrate the likely genotoxic potential of the use of IVM in cattle.”

“Regardless of the IVM concentration, the presence of nuclei with DNA migration (Figure 1a and b) was observed at a percentage greater than 75% in all cells observed per plaque, demonstrating the ability of the IVM compound to produce simple chain breaks in the DNA molecule.”

The Comet classification describes how. All of the control group (no treatment) measure 0 on the comet scale. Here are the Results for the IVM treated cows:



Grade 3 = cells with high damage

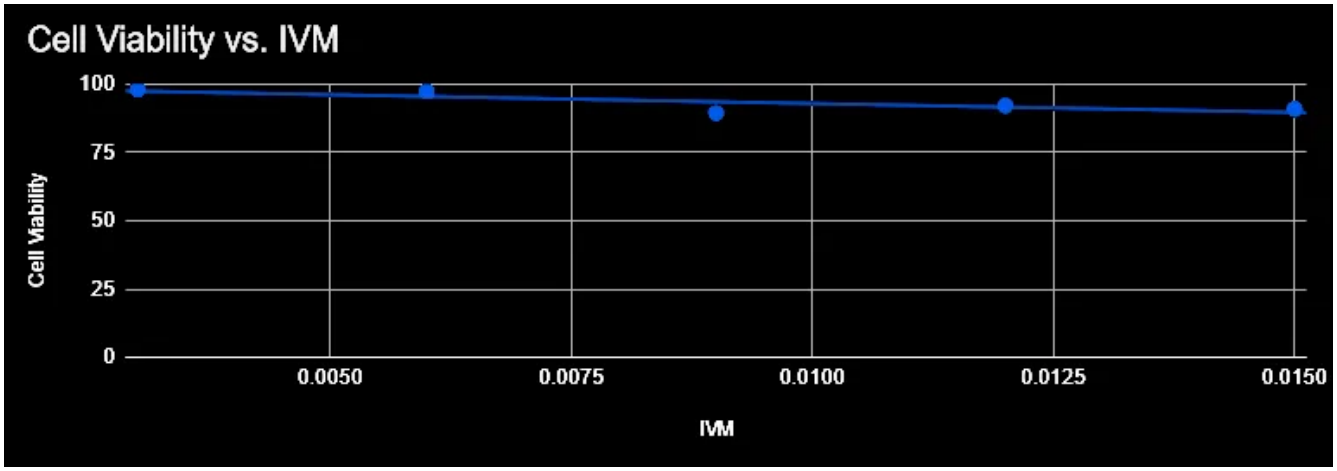
> "The results found in the present study constitute concrete evidence for the induction of genomic damage as exerted by IVM, using the comet assay methodology"

> "Ivermectin (20 pg/mL) decreased glucose utilization in IB-RS-2 cells in 11, 30, and 31%, respectively, after 24,48 and 72 h"

Ivermectin Vs Tadpole DNA

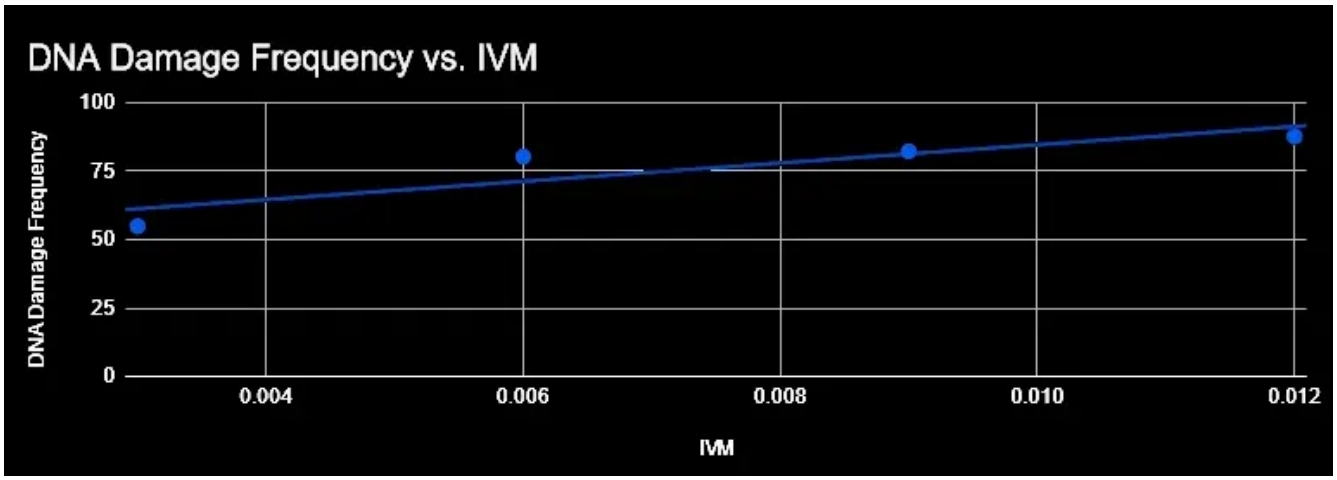
In a study called 'Genotoxicity of Three Avermectins on Polypedates megacephalus Tadpoles Using the Comet Assay' by Geng et al, some very concerning findings were noted in relation to Ivermectin's "genotoxic effects at relatively low concentrations" in Tadpoles.

The first chart shows a dose-dependent decline in cell viability as IVM dosing increases:



> "Our results showed clearly that avermectins caused dose dependent DNA damage on amphibian tadpoles… The three avermectins increased the DNA damage observed in the tadpoles in a dose-responsive manner. There were strong linear correlations between the DNA damages and the concentrations of the three test substances (Figure 2). The cellular distributions of DNA damages in tadpoles are shown in Figure 3. Of the tadpoles treated with increasing concentrations of the three test substances, higher proportions of cells had greater amount of DNA damage than those of the negative control"

This chart shows a dose-dependent increase in DNA damage as IVM dosing increases:



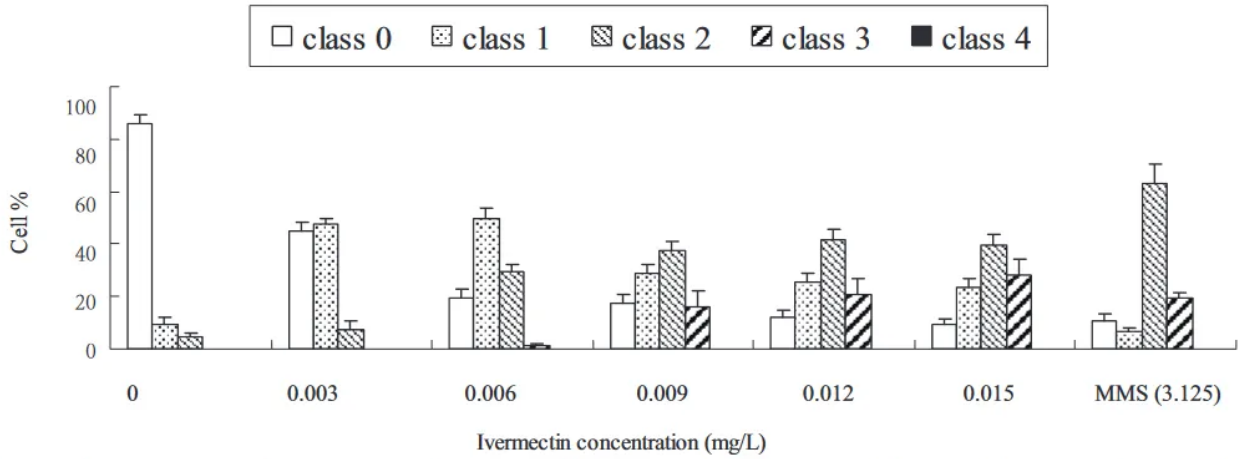


Figure 3 Distribution of DNA damage (based on damage class of DNA patterns pooled across 8 tadpoles in each dose group) observed at the cellular level in *Polypedates megacephalus* tadpoles after exposure for a 48 h period to selected concentrations of abamectin, ivermectin and emamectin benzoate.

> "According to these results above and our finding that avermectins can cause DNA damage in tadpoles at the concentrations below the recommended applied levels (Xu et al., 2010), we consider it possible that avermectins are carcinogenic, and confirm it has the negative impact on the development of tadpoles"

Ivermectin And Pig Kidney Cells

In a study entitled 'Toxicity Assessment of the Antiparasitic Ivermectin' by Rodrigues et al, the researchers exposed pig kidney cells to ivermectin at different levels and measured the rates of cell death (Full article)

> "Our data show that ivermectin inhibited cell growth (Fig. 1). This effect was time and dose dependent, and ranged from 38 to 84% after 72 h in cells treated with 2-20 pg/mL; at the dosage of 40 pg/mL, cell death occurred within 24 h."

> "Ivermectin (20 pg/mL) decreased protein synthesis and glucose utilization."

> "Protein synthesis is inhibited in a continuous way in the cells exposed to ivermectin (20 pg/mL). When compared to the control cultures, the protein of treated cells is 13,24, and 28% less, respectively, after 24, 48, and 72 h."

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