

COBALT, ANTIMONY COMPOUNDS, AND WEAPONS-GRADE TUNGSTEN ALLOY

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Table S4.6 Genetic and related effects of cobalt in non-mammalian experimental systems

Test system (species, strain)	End-point	Results ^a		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
<i>Cobalt metal</i>						
<i>Salmonella typhimurium</i> TA98	Reverse mutation	+	–	100 µg/plate	OECD 471.	NTP (2014)
<i>Salmonella typhimurium</i> TA100	Reverse mutation	+/-	–	5000 µg/plate	OECD 471.	NTP (2014)
<i>Escherichia coli</i> WP2 <i>uvrA</i>	Reverse mutation	–	–	200 µg/plate	OECD 471.	NTP (2014)
<i>Salmonella typhimurium</i> TA98	Reverse mutation	–	–	1000–5000 µg/plate	OECD 471, 3 individual studies, maximum doses: 1000, 5000, 5000 µg/plate.	Kirkland et al. (2015)
<i>Cobalt metal NPs</i>						
<i>Drosophila melanogaster</i>	Gene mutation or mitotic recombination, wing spot test <i>mwh/flr</i>	+	NA	5 mM		Vales et al. (2013)
<i>Drosophila melanogaster</i>	Gene mutation or mitotic recombination, wing spot test <i>mwh/TM3</i>	–	NA	10 mM		Vales et al. (2013)
<i>Drosophila melanogaster</i>	Gene mutation or mitotic recombination, wing spot test <i>mwh/flr</i>	+	NA	10 mM		Ertuğrul et al. (2020)
<i>Drosophila melanogaster</i>	DNA strand breaks, comet assay in <i>Drosophila</i> haemocytes	+	NA	0.1 mM		Ertuğrul et al. (2020)
<i>Soluble cobalt(II) salts</i>						
<i>Cobalt(II) chloride (hydrate not specified)</i>						
<i>Drosophila melanogaster</i>	Gene mutation or mitotic recombination, wing spot test <i>mwh/flr</i>	+	NA	2 mM [260 µg/mL]		Ogawa et al. (1994)
<i>Drosophila melanogaster</i>	Gene mutation or reduced mitotic recombination, wing spot test <i>mwh/TM3</i>	–	NA	8 mM [1040 µg/mL]		Ogawa et al. (1994)
<i>Saccharomyces cerevisiae</i> SBTD-2	“Petite” mutation, respiratory deficiency	+	NT	2 mM [260 µg/mL]		Prazmo et al. (1975)

Table S4.6 (continued)

Test system (species, strain)	End-point	Results ^a		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
<i>Saccharomyces cerevisiae</i> , strain 197/2d	“Petite” mutation	+	NT	4 mM [520 µg/mL]		Putrament et al. (1977)
<i>Saccharomyces cerevisiae</i> , strain 197/2d	Erythromycin-resistant mutation	–	NT	4 mM [520 µg/mL]		Putrament et al. (1977)
<i>Saccharomyces cerevisiae</i>	“Petite” mutation	+/-	NT	640 µg/mL		Egilsson et al. (1979)
<i>Saccharomyces cerevisiae</i> D7	<i>Ilv</i> gene mutation	–	NT	10 mM [1300 µg/mL]		Fukunaga et al. (1982)
<i>Saccharomyces cerevisiae</i> D7	<i>Trp</i> gene conversion	+	NT	10 mM [1300 µg/mL]		Fukunaga et al. (1982)
<i>Saccharomyces cerevisiae</i> D7	<i>Ilv</i> gene mutation	–	NT	100 mM [13 000 µg/mL]		Singh (1983)
<i>Saccharomyces cerevisiae</i> D7	<i>Trp</i> gene conversion	+/-	NT	100 mM [13 000 µg/mL]		Singh (1983)
<i>Saccharomyces cerevisiae</i> D7	<i>Trp</i> gene conversion	+	NT	11.5 mM [1500 µg/mL]		Kharab & Singh (1985)
<i>Saccharomyces cerevisiae</i> D7	<i>Ilv</i> gene mutation	+/-	NT	23 mM [3000 µg/mL]		Kharab & Singh (1985)
<i>Saccharomyces cerevisiae</i> D7	“Petite” mutation, respiratory deficiency	+	NT	5.76 mM [750 µg/mL]		Kharab & Singh (1987)
<i>Salmonella typhimurium</i> TA100, TA98	Reverse mutation	(–)	NT	NR	Test doses and data, NR.	Ogawa et al. (1986)
<i>Salmonella typhimurium</i> TA102	Reverse mutation	–	–	40 ppm [40 µg/mL]		Wong (1988)
<i>Salmonella typhimurium</i> TA1535, TA1537, TA1538, TA98	Reverse mutation	(–)	NT	NR	Test doses, NR.	Arlauskas et al. (1985)
<i>Salmonella typhimurium</i> TA1535	Reverse mutation	–	–	40 ppm [40 µg/mL]		Wong (1988)
<i>Salmonella typhimurium</i> TA1537 and TA2637	Reverse mutation	–	NT	1000 µmol/plate [130 µg/plate]		Ogawa et al. (1986)

Table S4.6 (continued)

Test system (species, strain)	End-point	Results ^a		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
<i>Salmonella typhimurium</i> TA98 and TA1537	Reverse mutation	+	-	40 ppm [40 µg/mL]		Wong (1988)
<i>Salmonella typhimurium</i> TA97	Reverse mutation	+	NT	100 µM [13 µg/mL]	Pre-incubation assay	Pagano & Zeiger (1992)
<i>Escherichia coli</i> WP2s(λ)	Prophage induction	-	NT	320 µM [41.5 µg/mL]		Rossman et al. (1984)
<i>Escherichia coli</i> SY1032/pKY241 transfected with pUB3, <i>supF</i> tRNA locus	Mutation	+	NT	20 µM [2.6 µg/mL]		Ogawa et al. (1999)
<i>Bacillus subtilis</i> rec strain H17/M45	Growth inhibition	-	NT	50 mM [325 µg/plate]		Nishioka (1975)
<i>Bacillus subtilis</i> rec strain H17	Growth inhibition	+	NT	50 mM [325 µg/plate]		Kanematsu et al. (1980)
<i>Cobalt(II) chloride hexahydrate (CoCl₂·6H₂O)</i>						
<i>Danio rerio</i> , male zebrafish	DNA strand breaks in sperm, comet assay	(+)	NA	5 mg/L	Positive only when measured immediately after exposure, damage did not differ from controls after 6 h recovery period.	Reinardy et al. (2013)
<i>Eisenia hortensis</i> , earthworms	DNA strand breaks in coelomocytes, comet assay	+	NA	NR	226 ppm in water administered 3×/wk, this dose represented the LD ₅₀ .	Çiğerci et al. (2016)
<i>Eisenia hortensis</i> , earthworms	Micronuclei in coelomocytes	+	NA	NR	No total dose given, 113 ppm in water administered per week (represented LD ₅₀ /2, other levels tested represented LD ₅₀ and 2 × LD ₅₀ levels).	Çiğerci et al. (2016)
<i>Drosophila melanogaster</i>	Gene mutation or mitotic recombination, wing spot test <i>mwh/flr</i>	+	NA	10 mM [2.4 µg/mL]	Effect observed only at the highest dose.	Vales et al. (2013)
<i>Drosophila melanogaster</i>	Gene mutation or mitotic recombination, wing spot test <i>mwh/flr</i>	(+)	NA	8 mM	One dose tested.	Kaya et al. (2002)

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Test system (species, strain)	End-point	Results ^a		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
<i>Drosophila melanogaster</i>	Gene mutation or mitotic recombination, wing spot test <i>mwh/flr</i>	(+)	NA	8 mM	One dose tested.	Demir et al. (2009)
<i>Drosophila melanogaster</i>	Gene mutation or mitotic recombination, wing spot test <i>mwh/flr</i>	+	NA	10 mM		Ertuğrul et al. (2020)
<i>Drosophila melanogaster</i>	DNA strand breaks, comet assay in <i>Drosophila</i> haematocytes	+	NA	0.1 mM		Ertuğrul et al. (2020)
<i>Allium cepa</i> L.	Chromosomal aberrations	+	NA	5.5 ppm [5.5 mg/L]	A significant decrease in mitotic index observed at the doses studied.	Yıldız et al. (2009)
<i>Allium cepa</i> L.	DNA strand breaks, comet assay	+	NA	5.5 ppm [Zeiger 5.5 mg/L]	A significant decrease in mitotic index observed at the doses studied.	Yıldız et al. (2009)
<i>Saccharomyces cerevisiae</i> D7	“Petite” mutation, respiratory deficiency	+	NT	[130 µg/mL]		Lindegren et al. (1958)
<i>Escherichia coli</i> WP2	Reverse mutation	–	NT	20 µg/mL	Antimutagenic effect observed.	Kada & Kanematsu (1978)
<i>Escherichia coli</i> WP2 <i>uvrA</i>	Reverse mutation	(–)	NT	NR	Test doses NR.	Arlauskas et al. (1985)
<i>Salmonella typhimurium</i> TA100	Reverse mutation	–	NT	100 mM [23 800 µg/mL]		Tso & Fung (1981)
<i>Salmonella typhimurium</i> TA100	Reverse mutation	(–)	NT	NR	Test doses NR, apparently strains TA98, TA1535, and TA1537 were also tested without response.	Arlauskas et al. (1985)
<i>Salmonella typhimurium</i> TA1538, TA98	Reverse mutation	–	NT	84 µM [20 µg/mL]	Inhibition of mutagenesis induced by Trp-P-1.	Mochizuki & Kada (1982)

Table S4.6 (continued)

Test system (species, strain)	End-point	Results ^a		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
<i>Salmonella typhimurium</i> TA97a	Reverse mutation	–	–	3160–5000 µg/plate	OECD 471, 3 individual studies, maximum doses: 3160, 5000, 5000 µg/plate.	Kirkland et al. (2015)
<i>Salmonella typhimurium</i> TA1535/ <i>pSK1002</i>	<i>umu-c</i> test	–	–	6.8 µM [1.6 µg/mL]		Yamamoto et al. (2002)
<i>Bacillus subtilis</i> strain NIG 1125	Reverse mutation	–	NT	30 µg/mL [126 µM]	Inhibition of spontaneous mutations.	Inoue et al. (1981)
<i>Cobalt(II) nitrate (Co(NO₃)₂)</i> <i>Pisum abyssinicum</i> chlorophyll	Mutation	(+)	NA	0.1–1 mM	Nitrate salt of cobalt used, unclear if cobalt(II) or cobalt(III) nitrate.	Von Rosen (1964)
<i>Cobalt(II) nitrate hexahydrate (Co(NO₃)₂·6H₂O)</i> <i>Drosophila melanogaster</i>	Gene mutation, chromosomal deletion, non-disjunction, or mitotic recombination (wing spot test <i>mwh/flr</i> , small single spots and large single spots) SMART test	+	NA	1 mM [291 µg/mL]		Yeşilada (2001)
<i>Drosophila melanogaster</i>	Mitotic recombination (wing spot test <i>mwh/flr</i> , twin spots), SMART test	+	NA	10 mM [2910 µg/mL]		Yeşilada (2001)
<i>Allium cepa</i> L.	Chromosomal aberrations, micronuclei	(+)	NA	5.5 mg/L cobalt(II) nitrate hexahydrate	One dose only, significant decrease in mitotic index observed.	Kalefetoğlu Macar et al. (2021); Macar et al. (2020)
<i>Zea mays</i> L.	DNA damage, RAPD technique	+	NA	5 mM [1455 mg/L] cobalt(II) nitrate hexahydrate		Erturk et al. 2013
<i>Cobalt(II) sulfate (CoSO₄)</i> <i>Allium cepa</i>	Chromosomal aberrations	+	NA	20 µM [3 µg/mL]		Gori & Zucconi (1957)
<i>Allium cepa</i>	Aneuploidy	+	NA	100 µM [15 µg/mL] for 5 d + H ₂ O for 3 d		Gori & Zucconi (1957)

Table S4.6 (continued)

Test system (species, strain)	End-point	Results ^a		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
<i>Escherichia coli</i>	DNA strand breaks, pulse field gel electrophoresis	+	NT	0.5 mM	In addition, inhibition of SOS repair pathways was observed.	Kumar et al. (2017)
<i>Bacillus subtilis</i> rec strain H17	Growth inhibition	+/-	NT	50 mM [388] µg/plate		Kanematsu et al. (1980)
<i>Cobalt(II) sulfate heptahydrate (CoSO₄·7H₂O)</i>						
<i>Salmonella typhimurium</i> TA100	Reverse mutation	+	-	100 µg/plate	+ S9: tested at doses up to 10 000 µg/plate.	Zeiger et al. (1992)
<i>Salmonella typhimurium</i> TA98, TA1535	Reverse mutation	-	-	10 000 µg/plate		Zeiger et al. (1992)
<i>Salmonella typhimurium</i> TA100	Reverse mutation	-	-	5000 µg/plate	OECD 471, 3 individual studies.	Kirkland et al. (2015)
<i>Cobalt(II) acetate tetrahydrate (Co(CH₃CO₂)₂·4H₂O)</i>						
<i>Escherichia coli</i> WP2	Reverse mutation	+	-	250 µg/plate		Maeda et al. (2021)
<i>Insoluble cobalt(II or II,III) compounds</i>						
<i>Cobalt(II,III) oxide NPs</i>						
<i>Solanum melongena</i> L. cv. Violetta lunga 2, eggplant	DNA strand breaks, comet assay	(+)	NA	0.25 mg/mL	Also significant induction of apoptosis observed.	Faisal et al. (2016)
<i>Salmonella typhimurium</i> TA98	Reverse mutation	-	NT	500 µg/mL	Two sizes tested, on average 10–30 nm and 80–150 nm.	Kong et al. (2020)
<i>Organic cobalt(II) compounds</i>						
<i>Salmonella typhimurium</i> TA98, TA100, TA102, TA1535, TA1537	Reverse mutation	-	-	1000 µg/plate	Guideline-based study, cobalt(II) acetyl acetate.	Kirkland et al. (2015)
<i>Salmonella typhimurium</i> TA98, TA100, TA102, TA1535, TA1537	Reverse mutation	-	-	1000 µg/plate	Guideline-based study, cobalt(II) resinate.	Kirkland et al. (2015)

HIC, highest ineffective concentration; LD₅₀, median lethal dose; LEC, lowest effective concentration; NA, not applicable; NR, not reported; NT, tested; OECD, Organisation for Economic Co-operation and Development; ppm, parts per million; RAPD, randomly amplified polymorphic DNA; S9, 9000 × g supernatant; SMART, somatic mutation and recombination test; tRNA, transfer RNA; Trp-P-1, 3-amino-1,4-dimethyl-5H-pyridol[4,3-B]indole; wk, week.

^a +, positive; -, negative; +/-, equivocal (variable response in several experiments within an adequate study); (+) or (-), positive or negative in a study of limited quality.

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