

**COBALT,
ANTIMONY COMPOUNDS,
AND WEAPONS-GRADE
TUNGSTEN ALLOY**

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OF CARCINOGENIC HAZARDS
TO HUMANS**

Table S4.14 Oxidative stress in non-human mammals in vivo exposed to cobalt

End-point	Species, strain, (sex)	Tissue	Results ^a	Direction of response	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
<i>Cobalt metal</i>								
Lipid peroxides, GSH, AOPP	Rat, SD (M)	Serum	–	No changes	1 cylinder of 1 mm in diameter by 2 mm in length/rat	Metal pellet implantation	Multiple time points tested following implantation.	Kalinich et al. (2022)
<i>Cobalt(II) chloride (CoCl₂)</i>								
MDA and/or HNE adduct formation	Rabbit, Albino (M)	Blood (erythrocyte and plasma)	+	↑	25 mg/kg [bw]/day	Subcutaneous, 3 days, 1×/day	A single dose tested with reasonable sample size.	Kuno et al. (1980)
	Rabbit, White (M)	Blood (erythrocyte and plasma)	+	↑	25 mg/kg [bw]/day	Subcutaneous, 3 days, 1×/day	A single dose tested with reasonable sample size.	Morita et al. (1982)
	Guinea-pig (M)	Liver	+	↑	80 mg/kg [bw]	Subcutaneous, 24 h, single dose	A single dose tested; Multiple end-points detected.	Christova et al. (2002)
	Rat, Wistar (M)	Liver	+	↑	10–60 mg/kg [bw]/day	Subcutaneous, 1–6 days, 1×/day	Multiple doses and durations tested. A single dose tested; Multiple end-points detected.	Christova et al. (2001) Christova et al. (2002)
		Cardiac and renal tissues	+	↑	150, 300, 600 ppm	Oral administration (in drinking-water), 7 days	Dose-dependent effect.	Oyagbemi et al. (2019)
		Brain	+	↑	150 mg/kg [bw]/day	Oral gavage, 7 days, 1×/day, single dose	A single dose tested; Multiple end-points detected.	Akinrinde & Adebiyi (2019)
	Rat, Wistar (F)	Liver	+	↑	30 mg/kg [bw]	Intraperitoneal injection, 2 h, single dose	A single dose tested with reasonable sample size.	Sumbayev (2001)
					375 µmol/kg [bw]	Subcutaneous, 0–40 h, single dose	Time-dependent effect; CoCl ₂ used as an oxidative stress inducer.	Gonzales et al. (2005)
	Rat, Wistar (F, pregnant and lactating)	F ₀ and F ₁ liver	+	↑	350 ppm	Oral administration (in drinking-water), started from day 14 of gestation until day 14 after delivery	A single dose tested; multiple end-points detected.	Garoui et al. (2011)
		Progeny cerebrum and cerebellum	+	↑	350 ppm	Oral administration (in drinking-water), started from day 14 of gestation until day 14 after delivery	A single dose tested; multiple end-points detected.	Garoui et al. (2013)

Table S4.14 (continued)

End-point	Species, strain, (sex)	Tissue	Results ^a	Direction of response	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
MDA and/or HNE adduct formation (cont.)	Rat, SD (M)	Brain	+	↑	50 mg/kg [bw]/day	Intragastric, 7 days, 1×/day	Cobalt prevents hypoxia-induced oxidative stress.	Shrivastava et al. (2008)
	Mouse, BDF ₁ (M)	Liver	+	↑	60 mg/kg [bw]	Subcutaneous, 24 h, single dose	A single dose tested; multiple end-points detected.	Christova et al. (2003)
MDA	Rat, SD (M)	Red gastrocnemius muscle and plasma	+	↓	10 mg/kg [bw]/day (LED, 10 mg/kg [bw])	Oral administration, 15 days, 1×/day	CoCl ₂ ·6H ₂ O used as hypoxia pre-treatment; a single dose tested with reasonable sample size; Multiple end-points detected.	Saxena et al. (2010)
Superoxide level	Rabbit, White (M)	Blood (erythrocyte and plasma)	+	↑	25 mg/kg [bw]/day	Subcutaneous, 3 days, 1×/day	A single dose tested with reasonable sample size.	Morita et al. (1982)
	Rabbit (M)	Alveolar macrophages in lung	+	↑	Cobalt: 0.4–2 µg/L	Inhalation, 14–16 wk (5 days/wk, 6 h/day)	Multiple doses test with reasonable sample size.	Johansson et al. (1986)
H ₂ O ₂ level	Rat, Wistar (M)	Cardiac and renal tissues	+	↑	150–600 ppm	Oral administration (in drinking-water), 7 days	Dose-dependent effect.	Oyagbemi et al. (2019)
	Rat, Wistar (F)	Liver	(+)	↑	370 µmol/kg [bw]	Subcutaneous, 0–48 h, single dose	Time-dependent effect but no statistical difference.	Llesuy & Tomaro (1994)
	Rat, Wistar (M + F)	Brain	+	↑	150 mg/kg [bw]/day	Oral gavage, 7 days, 1×/day, single dose	A single dose tested; multi end-points detected.	Akinrinde & Adebisi (2019)
	Rat, Wistar (F, pregnant and lactating)	Progeny cerebrum and cerebellum	+	↑	350 ppm	Oral administration (in drinking-water), started from day 14 of gestation until day 14 after delivery	A single dose tested; multiple end-points detected.	Garoui et al. (2013)
	Rat, SD (M)	Liver microsome	(+)	↓	30 mg/kg [bw]/day	Subcutaneous, 3 days, 1×/day	A single dose tested; limited samples (<i>n</i> = 2–6).	Daido & Aniya (1994)

Table S4.14 (continued)

End-point	Species, strain, (sex)	Tissue	Results ^a	Direction of response	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
NO level	Rat, Wistar (M)	Liver	+	↑	150–600 mg/L	Oral administration (in drinking-water), 7 days	Dose-dependent effect.	Awoyemi et al. (2017)
	Rat, Wistar (M + F)	Brain	+	↑	150 mg/kg [bw]/day	Oral gavage, 7 days, 1×/day, single dose	A single dose tested; multiple end-points detected.	Akinrinde & Adebiyi (2019)
	Rat, Wistar (M)	Cortex, cerebellum, and hippocampus	(+)	↑	Cobalt: 12.5 mg/kg [bw]/day	Oral administration, 7 days, 1×/day	CoCl ₂ used as hypoxia mimic preconditioning.	Kalpana et al. (2008)
		Cardiac and renal tissues	+	↑	650 ppm	Oral administration (in drinking-water), 14 days	A single dose tested; Combination with antioxidant drugs.	Ajibade et al. (2017)
AOPP level	Wistar rats (M)	Liver	+	↑	150–600 mg/L	Oral administration (in drinking-water), 7 days	Dose-dependent effect.	Awoyemi et al. (2017)
		Cardiac and renal tissues	+	↑	150–600 ppm	Oral administration (in drinking-water), 7 days	Dose-dependent effect.	Oyagbemi et al. (2019)
	Rat, Wistar (F, pregnant and lactating)	Progeny cerebrum and cerebellum	+	↑	350 ppm	Oral administration (in drinking-water), started from the 14th days of pregnancy until day 14 after delivery	A single dose tested; multiple end-points detected.	Garoui et al. (2013)
ROS level	Rat, SD (M)	Brain	+	↓	50 mg/kg [bw]/day	Intragastric, 7 days, 1×/day	Cobalt prevents hypoxia-induced oxidative stress.	Shrivastava et al. (2008)
	Rat, Wistar (M)	Cortex, cerebellum, and hippocampus	(+)	↓	12.5 mg [bw]/day	Oral administration, 7 days, 1×/day	CoCl ₂ used as hypoxia mimic preconditioning.	Kalpana et al. (2008)
PC level	Rat, Wistar (F, pregnant and lactating)	Progeny cerebrum and cerebellum	+	↑	350 ppm	Oral administration (in drinking-water), started from day 14 of gestation until day 14 after delivery	A single dose tested; multiple end-points detected including reduced V _c level.	Garoui et al. (2013)
	Rat, SD (M)	Brain	+	↓	50 mg/kg [bw]/day	Intragastric, 7 days, 1×/day	Cobalt prevents hypoxia-induced oxidative stress.	Shrivastava et al. (2008)

Table S4.14 (continued)

End-point	Species, strain, (sex)	Tissue	Results ^a	Direction of response	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
HO activity	Guinea-pig (M)	Liver	+	↑	80 mg/kg [bw]	Subcutaneous, 24 h, single dose	A single dose tested; multiple end-points detected.	Christova et al. (2002)
	Rat, Wistar (M)	Liver	+	↑	Cobalt: 125–375 µmol/kg [bw]	Subcutaneous, 1–24 h, single or multiple doses	Dose- and time interval-dependent effects; different repeated dosages effect; multiple administrations effect.	Numazawa et al. (1989a)
	Rat, Wistar (F)	Liver	(+) +	↑	10–60 mg/kg [bw]/day	Subcutaneous, 1–6 days, 1×/day	Multiple doses and durations were tested.	Christova et al. (2001)
					60 mg/kg [bw]	Subcutaneous, 24 h, single dose	A single dose tested; multiple end-points detected.	Christova et al. (2002)
					370 µmol/kg [bw]	Subcutaneous, 0–48 h, single dose	Time-dependent effect but no statistical difference.	Llesuy & Tomaro (1994)
	Rat, SD (M)	Liver	+	↑	375 µmol/kg [bw]	Subcutaneous, 0–40 h, single dose	A single dose tested; CoCl ₂ used as an oxidative stress inducer.	Gonzales et al. (2005)
					60 mg/kg [bw]/day	Subcutaneous, 2 days, 1×/day	A single dose tested; limited sample size (<i>n</i> = 3).	Maines & Kappas (1974)
					250 µmol/kg [bw]	Subcutaneous, 4–48 h, single dose	CoCl ₂ used as a potent inducer of HO; different duration was tested.	Kappas et al. (1985)
GPX activity	Mouse, BDF ₁ (M)	Liver	+	↑	60 mg/kg [bw]	Subcutaneous, 24 h, single dose	A single dose tested; multiple end-points detected.	Christova et al. (2003)
	Guinea-pig (M)	Liver	+	↓	80 mg/kg [bw]	Subcutaneous, 24 h, single dose	A single dose tested; multiple end-points detected.	Christova et al. (2002)
	Mouse, BDF ₁ (M)	Liver	+	↓	60 mg/kg [bw]	Subcutaneous, 24 h, single dose	A single dose tested; multiple end-points detected.	Christova et al. (2003)
	Rat, Wistar (M)	Myocardium	+	↓	1–50 mg/kg [bw]/day	Subcutaneous, 8 days, 1×/day	Dose-dependent effect.	Hatori et al. (1993)

Table S4.14 (continued)

End-point	Species, strain, (sex)	Tissue	Results ^a	Direction of response	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
GPX activity (cont.)	Rat, Wistar (M)	Liver	+	↓	10–60 mg/kg [bw]/day 150–600 mg/L	Subcutaneous, 1–6 days, 1×/day Oral administration (in drinking-water), 7 days	Multiple doses and durations tested. Dose-dependent effect.	Christova et al. (2001) Awoyemi et al. (2017)
		Cardiac and renal tissues	+	↓	650 ppm	Oral administration (in drinking-water), 14 days	A single dose tested; combination with antioxidant drugs.	Ajibade et al. (2017)
					150–600 ppm	Oral administration (in drinking-water), 7 days	Dose-dependent effect.	Oyagbemi et al. (2019)
	Rat, Wistar (M + F)	Brain	+	↓	150 mg/kg [bw]/day	Oral gavage, 7 days, 1×/day, single dose	A single dose tested; Multiple end-points detected.	Akinrinde & Adebisi (2019)
	Rat, Wistar (F)	Liver	(+)	↓	370 µmol/kg [bw]	Subcutaneous, 0–48 h, single dose	Time-dependent effect but no statistical difference.	Llesuy & Tomaro (1994)
			+	↓	375 µmol/kg [bw]	Subcutaneous, 12 h, single dose	A single dose tested; CoCl ₂ used as an oxidative stress inducer.	Gonzales et al. (2005)
	Rat, Wistar (F, pregnant and lactating)	F ₀ and F ₁ liver	+	↓	350 ppm	Oral administration (in drinking-water), started from day 14 of gestation until day 14 after delivery	A single dose tested; multiple end-points detected.	Garoui et al. (2011)
	Rat, Wistar (F, pregnant and lactating)	Progeny cerebrum and cerebellum	+	↓	350 ppm	Oral administration (in drinking-water), started from day 14 of gestation until day 14 after delivery	A single dose tested; multiple end-points detected.	Garoui et al. (2013)
	Rat, SD (M)	Liver microsome	+	↓	30 mg/kg [bw]/day 30–60 mg/kg [bw]/day	Subcutaneous, 0–24 h, single dose Subcutaneous, 3 days, 1×/day	Time-dependent effects. Dose-dependent effects.	Daido & Aniya (1994) Daido & Aniya (1994)
		Brain	+	↓	50 mg/kg [bw]/day	Intragastric, 7 days, 1×/day	Cobalt prevents hypoxia-induced oxidative stress.	Shrivastava et al. (2008)

Table S4.14 (continued)

End-point	Species, strain, (sex)	Tissue	Results ^a	Direction of response	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
GPX activity (cont.)		Red gastrocnemius muscle	+	↓	10 mg/kg [bw]/day (LED, 10 mg/kg [bw])	Oral administration, 15 days	CoCl ₂ ·6H ₂ O used as hypoxia pre-treatment; a single dose tested with reasonable sample size; Multiple end-points detected.	Saxena et al. (2010)
GST activity	Rat, SD (M)	Liver microsome	+	↑	30–60 mg/kg [bw]/day 60 mg/kg [bw]	Subcutaneous, 3 days, 1×/day Subcutaneous, 0–24 h, single dose	Dose-dependent effect. Time-dependent effect.	Daido & Aniya (1994) Daido & Aniya (1994)
	Rat, Wistar (M)	Liver	+	↓	150–600 mg/L	Oral administration (in drinking-water), 7 days	Dose-dependent effect.	Awoyemi et al. (2017)
		Cardiac and renal tissues	+	↓	150–600 ppm [150–600 mg/L]	Oral administration (in drinking-water), 7 days	Dose-dependent effect.	Oyagbemi et al. (2019)
	Rats, SD (M)	Brain	+	↓	50 mg/kg [bw]/day	Intragastric, 7 days, 1×/day	Cobalt prevents hypoxia-induced oxidative stress.	Shrivastava et al. (2008)
SOD activity	Guinea-pig (M)	Liver	+	↓	80 mg/kg [bw]	Subcutaneous, 24 h, single dose	A single dose tested; Multiple end-points detected.	Christova et al. (2002)
	Rat, Wistar (M)	Liver	+	↓	10–60 mg/kg [bw]/day 150–600 mg/L	Subcutaneous, 1–6 days, 1×/day Oral administration (in drinking-water), 7 days	Multiple doses and durations were tested. Dose-dependent effect.	Christova et al. (2001) Awoyemi et al. (2017)
		Brain	+	↓	40 mg/kg [bw]/day	Oral gavage, 60 days, 1×/day, single dose	CoCl ₂ used as hypoxia mimic; a single dose tested; multiple end-points detected.	Abdel-Rahman Mohamed et al. (2019)
	Rat, Wistar (F)	Liver	(+)	↓	370 µmol/kg [bw]	Subcutaneous, 0–48 h, single dose	Time-dependent effect but no statistical difference.	Llesuy & Tomaro (1994)
			+	↓	375 µmol/kg [bw]	Subcutaneous, 12 h, single dose	A single dose tested; CoCl ₂ used as an oxidative stress inducer.	Gonzales et al. (2005)

Table S4.14 (continued)

End-point	Species, strain, (sex)	Tissue	Results ^a	Direction of response	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
SOD activity (cont.)	Rat, Wistar (F, pregnant and lactating)	F ₀ and F ₁ liver	+	↓	350 ppm	Oral administration (in drinking-water), started from day 14 of gestation until day 14 after delivery	A single dose tested; Multiple end-points detected.	Garoui et al. (2011)
		Progeny cerebrum and cerebellum	+	↓	350 ppm	Oral administration (in drinking-water), started from day 14 of gestation until day 14 after delivery	A single dose tested; multiple end-points detected.	Garoui et al. (2013)
	Rat, Wistar (M + F)	Brain	+	↓	150 mg/kg [bw]/day	Oral gavage, 7 days, 1×/day, single dose	A single dose tested; multiple end-points detected.	Akinrinde & Adebisi (2019)
	Rat, SD (M)	Brain	+	↓	50 mg/kg [bw]/day	Intragastric, 7 days, 1×/day	Cobalt prevents hypoxia-induced oxidative stress.	Shrivastava et al. (2008)
	Mouse, BDF ₁ (M)	Liver	+	↓	60 mg/kg [bw]	Subcutaneous, 24 h, single dose	A single dose tested; multiple end-points detected.	Christova et al. (2003)
Mn-SOD activity	Rat, Wistar (M)	Myocardium	+	↓	1–50 mg/kg [bw]/day	Subcutaneous, 8 days, 1×/day	Dose-dependent effect.	Hatori et al. (1993)
CAT activity	Guinea-pig (M)	Liver	+	↑	80 mg/kg [bw]	Subcutaneous, 24 h, single dose	A single dose tested; multiple end-points detected.	Christova et al. (2002)
	Rat, Wistar (M)	Liver	+	↓	10–60 mg/kg [bw]/day	Subcutaneous, 1–6 days, 1×/day	Multiple doses and durations tested.	Christova et al. (2001)
					150–600 mg/L	Oral administration (in drinking-water), 7 days	Dose-dependent effect.	Awoyemi et al. (2017)
		Brain	+	↓	40 mg/kg [bw]/day	Oral gavage, 60 days, 1×/day, single dose	CoCl ₂ used as hypoxia mimic; a single dose tested; multiple end-points detected.	Abdel-Rahman Mohamed et al. (2019)
		Cardiac and renal tissues	+	↓	150–600 ppm	Oral administration (in drinking-water), 7 days	Dose-dependent effect.	Oyagbemi et al. (2019)
	Rat, Wistar (F)	Liver	(+)	↓	370 µmol/kg [bw]	Subcutaneous, 0–48 h, single dose	Time-dependent effect but no statistical difference.	Llesuy & Tomaro (1994)
			+	↓	375 µmol/kg [bw]	Subcutaneous, 12 h, single dose	A single dose tested; CoCl ₂ used as an oxidative stress inducer.	Gonzales et al. (2005)

Table S4.14 (continued)

End-point	Species, strain, (sex)	Tissue	Results ^a	Direction of response	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
CAT activity (cont.)	Rat, Wistar (F, pregnant and lactating)	F ₀ and F ₁ liver	+	↓	350 ppm	Oral administration (in drinking-water), started from day 14 of gestation until day 14 after delivery	A single dose tested; Multiple end-points detected.	Garoui et al. (2011)
		Progeny cerebrum and cerebellum	+	↓	350 ppm	Oral administration (in drinking-water), started from day 14 of gestation until day 14 after delivery	A single dose tested; multiple end-points detected.	Garoui et al. (2013)
	Mouse, BDF ₁ (M)	Liver	+	↓	60 mg/kg [bw]	Subcutaneous, 24 h, single dose	A single dose tested; multiple end-points detected.	Christova et al. (2003)
GR activity	Guinea-pig (M)	Liver	+	↑	80 mg/kg [bw]	Subcutaneous, 24 h, single dose	A single dose tested; multiple end-points detected.	Christova et al. (2002)
	Rat, Wistar (M)	Liver	+	↑	10–60 mg/kg [bw]/day	Subcutaneous, 1–6 days, 1×/day	Multiple doses and durations were tested.	Christova et al. (2001)
					60 mg/kg [bw]	Subcutaneous, 24 h, single dose	A single dose tested; multiple end-points detected.	Christova et al. (2002)
GSH level	Rat, Wistar (M)	Liver	+	↑	10–30 mg/kg [bw]/day	Subcutaneous, 2–6 days, 1×/day	Multiple doses and durations tested	Christova et al. (2001)
	Rat, SD (M)	Liver	+	↑	45 mg/kg [bw]	Subcutaneous, single dose after fasted for 48 h	CoCl ₂ used to regulate GSH content; set the contrast.	Nordström et al. (1990)
		Red gastrocnemius muscle	+	↑	10 mg/kg [bw]/day (LED, 10 mg/kg [bw])	Oral administration, 15 days, 1×/day	CoCl ₂ ·6H ₂ O used as hypoxia pre-treatment; a single dose tested with reasonable sample size; multiple end-points detected.	Saxena et al. (2010)
	Guinea-pig (M)	Liver	+	↓	80 mg/kg [bw]	Subcutaneous, 24 h, single dose	A single dose tested; multiple end-points detected.	Christova et al. (2002)
	Rat, Wistar (M)	Liver	+	↓	60 mg/kg [bw]/day	Subcutaneous, 1 day, 1×/day	Multiple doses and duration tested.	Christova et al. (2001)
		Cardiac and renal tissues	+	↓	650 ppm	Oral administration (in drinking-water), 14 days	A single dose tested; combination with antioxidant drugs.	Ajibade et al. (2017)
					150–600 ppm	Oral administration (in drinking-water), 7 days	Dose-dependent effect.	Oyagbemi et al. (2019)

Table S4.14 (continued)

End-point	Species, strain, (sex)	Tissue	Results ^a	Direction of response	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
GSH level (cont.)		Brain	+	↓	40 mg/kg [bw]/day	Oral gavage, 60 days, 1×/day, single dose	CoCl ₂ used as hypoxia mimic; a single dose tested; multiple end-points detected.	Abdel-Rahman Mohamed et al. (2019)
	Rat, Wistar (F)	Liver	+	↓	375 µmol/kg [bw]	Subcutaneous, 0–40 h, single dose	Time-dependent effect; CoCl ₂ used as an oxidative stress inducer.	Gonzales et al. (2005)
	Rat, Wistar (F, pregnant and lactating)	F0 and F1 liver	+	↓	350 ppm	Oral administration (in drinking-water), started from day 14 of gestation until day 14 after delivery	A single dose tested; multiple end-points detected.	Garoui et al. (2011)
		Progeny cerebrum and cerebellum	+	↓	350 ppm	Oral administration (in drinking-water), started from day 14 of gestation until day 14 after delivery	A single dose tested; multiple end-points detected.	Garoui et al. (2013)
	Rat, Wistar (M + F)	Brain	+	↓	150 mg/kg [bw]/day	Oral gavage, 7 days, 1×/day, single dose	A single dose tested; multiple end-points detected.	Akinrinde & Adebisi (2019)
	Rat, SD (M)	Brain	+	↓	50 mg/kg [bw]/day	Intragastric, 7 days, 1×/day	Cobalt prevents hypoxia-induced oxidative stress.	Shrivastava et al. (2008)
	Mouse, BDF ₁ (M)	Liver	+	↓	60 mg/kg [bw]	Subcutaneous, 24 h, single dose	A single dose tested; multiple end-points detected.	Christova et al. (2003)
	Rat, Wistar (F)	Liver	(+)	↓	370 µmol/kg [bw]	Subcutaneous, 0–48 h, single dose	Time-dependent effect but no statistical difference.	Llesuy & Tomaro (1994)
GSSG level	Rat, SD (M)	Brain	+	↓	50 mg/kg [bw]/day	Intragastric, 7 days, 1×/day	Cobalt prevents hypoxia-induced oxidative stress.	Shrivastava et al. (2008)
GSH/GSSG ratio	Rat, SD (M)	Brain	+	↑	50 mg/kg [bw]/day	Intragastric, 7 days, 1×/day	Cobalt prevents hypoxia-induced oxidative stress.	Shrivastava et al. (2008)
		Red gastrocnemius muscle	+	↑	10 mg/kg [bw]/day (LED, 10 mg/kg [bw])	Oral administration, 15 days	CoCl ₂ ·6H ₂ O used as hypoxia pre-treatment; a single dose tested with reasonable sample size; multiple end-points detected.	Saxena et al. (2010)
PSH level	Rat, Wistar (M)	Renal tissues	+	↑	150–600 ppm	Oral administration (in drinking-water), 7 days	Dose-dependent effect and peaks at 600 ppm.	Oyagbemi et al. (2019)

Table S4.14 (continued)

End-point	Species, strain, (sex)	Tissue	Results ^a	Direction of response	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
PSH level (cont.)	Rat, Wistar (M)	Cardiac and renal tissues	+	↓	650 ppm	Oral administration (in drinking-water), 14 days	A single dose tested; combination with antioxidant drugs.	Ajibade et al. (2017)
NPSH level	Rat, Wistar (M)	Cardiac and renal tissues	+	↓	650 ppm	Oral administration (in drinking-water), 14 days	A single dose tested; combination with antioxidant drugs.	Ajibade et al. (2017)
	Rat, Wistar (F, pregnant and lactating)	Progeny cerebrum and cerebellum	+	↓	350 ppm	Oral administration (in drinking-water), started from day 14 of gestation until day 14 after delivery	A single dose tested; multiple end-points detected.	Garoui et al. (2013)
HO-1 level	Rat, Wistar (F)	Liver	+	↑	375 µmol/kg [bw]	Subcutaneous, 0–40 h, single dose	A single dose tested; CoCl ₂ used as an oxidative stress induce.	Gonzales et al. (2005)
	SD rats (M)	Liver	+	↑	300 µmol/kg [bw]	Subcutaneous, 6 h, single dose	A single dose tested.	Bauer et al. (1998)
		Red gastrocnemius muscle	+	↑	10 mg/kg [bw]/day (LED, 10 mg/kg [bw])	Oral administration, 15 days, 1×/day	CoCl ₂ ·6H ₂ O used as hypoxia pre-treatment; a single dose tested with reasonable sample size; multiple end-points detected.	Saxena et al. (2010)
		Kidney	+	↑	20 mg/kg [bw]/day	Oral gavage, 4 wk, 1×/day, single dose	CoCl ₂ used as hypoxia mimic; a single dose tested.	Nordquist et al. (2015)
HO-2 level	SD rats (M)	Liver	+	↑	300 µmol/kg [bw]	Subcutaneous, 6 h, single dose	A single dose tested.	Bauer et al. (1998)
Cu/Zn-SOD level	SD rats (M)	Kidney	+	↑	20 mg/kg [bw]/day	Oral gavage, 4 wk, 1×/day, single dose	CoCl ₂ used as hypoxia mimic; a single dose tested.	Nordquist et al. (2015)
NOX2 level	Rat, Wistar (M)	Brain	+	↑	50 mmol/day	Surgically injected into brain, 1–5 days	CoCl ₂ used as hypoxia mimic.	Guan et al. (2015)
Nrf2 level	Rat, Wistar (M)	Brain	+	↓	50 mmol/day	Surgically injected into brain, 1–5 days	CoCl ₂ used as hypoxia mimic.	Guan et al. (2015)

Table S4.14 (continued)

End-point	Species, strain, (sex)	Tissue	Results ^a	Direction of response	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
<i>Cobalt(II) chloride hexahydrate (CoCl₂·6H₂O)</i>								
MDA	Rat, Wistar (M)	Kidneys, heart	+	↑	350 ppm	Oral administration (in drinking-water), 7 days	A single dose tested; multiple end-points detected.	Akinrinde et al. (2016)
		Hippocampus	+	↑	4 mg/kg [bw]/day	Intraperitoneal injection, 20 days, 1×/day	A single dose tested; multiple end-points detected.	Zheng et al. (2019)
		Liver	+	↑	150–600 mg/L	Oral administration (in drinking-water), 7 days	Dose-dependent effect.	Awoyemi et al. (2017)
		Cardiac and renal tissues	+	↑	150 mg/kg [bw]/day	Intragastric, 8 days, 1×/day	A single dose tested; multiple end-points detected.	Oyagbemi et al. (2020)
	Rat, SD (M)	Kidney	+	↑	300 mg/L	Oral administration (in drinking-water), 28 days	A single dose tested; multiple end-points detected.	Abdel-Daim et al. (2020)
H ₂ O ₂ level	Rat, Wistar (M)	Kidneys, heart	+	↑	350 ppm	Oral administration (in drinking-water), 7 days	A single dose tested; multiple end-points detected.	Akinrinde et al. (2016)
		Liver	+	↑	150–600 mg/L	Oral administration (in drinking-water), 7 days	Dose-dependent effect.	Awoyemi et al. (2017)
		Cardiac and renal tissues	+	↑	150 mg/kg [bw]/day	Intragastric, 8 days, 1×/day	A single dose tested; multiple end-points detected.	Oyagbemi et al. (2020)
	Rat, SD (M)	Kidney	+	↑	300 mg/L	Oral administration (in drinking-water), 28 days	A single dose tested; multiple end-points detected.	Abdel-Daim et al. (2020)
NO level	Rat, Wistar (M)	Cardiac tissues	+	↑	150 mg/kg [bw]/day	Intragastric, 8 days, 1×/day	A single dose tested; multiple end-points detected.	Oyagbemi et al. (2020)
	Rat, SD (M)	Kidney	+	↑	300 mg/L	Oral administration (in drinking-water), 28 days	A single dose tested; multiple end-points detected.	Abdel-Daim et al. (2020)
ROS level	Rat, SD (M)	Liver	+	↑	300 mg/L	Oral administration (in drinking-water), 28 days	A single dose tested; multiple end-points detected.	Khalil et al. (2020)
8-OHdG level	Rat, SD (M)	Kidney	+	↑	300 mg/L	Oral administration (in drinking-water), 28 days	A single dose tested; multiple end-points detected.	Abdel-Daim et al. (2020)
Free radical level	Rat, SD (M)	Blood	+	↑	50 mM	Intravenous injection, 40 min continuously (at a rate of 23.3 µL/min)	Time-dependent effects.	Wang et al. (1993)
TAC	Rat, SD (M)	Liver	+	↓	300 mg/L	Oral administration (in drinking-water), 28 days	A single dose tested; multiple end-points detected.	Khalil et al. (2020)
PC level	Rat, SD (M)	Liver	+	↑	300 mg/L	Oral administration (in drinking-water), 28 days	A single dose tested; multiple end-points detected.	Khalil et al. (2020)

Table S4.14 (continued)

End-point	Species, strain, (sex)	Tissue	Results ^a	Direction of response	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
HO activity	Rat, SD (M)	Liver and bile	+	↑	250 µmol/kg [bw]	Subcutaneous, 1–72 h, single dose	Time-dependent effect.	Stelzer & Klaassen (1985)
	Rat, Wistar	Liver	+	↑	3 mg/100 g [bw]	Subcutaneous, 2–24 h, single dose	A single dose tested with reasonable sample size.	Kaliman et al. (2001)
GPX activity	Rat, Wistar (M)	Cardiac and renal tissues	+	↓	150 mg/kg [bw]/day	Intragastric, 8 days, 1×/day	A single dose tested; multiple end-points detected.	Oyagbemi et al. (2020)
GST activity	Rat, Wistar (M)	Heart	+	↑	350 ppm	Oral administration (in drinking-water), 7 days	A single dose tested; multiple end-points detected.	Akinrinde et al. (2016)
	Rat, Wistar (M)	Renal tissues	+	↓	150 mg/kg [bw]/day	Intragastric, 8 days, 1×/day	A single dose tested; multiple end-points detected.	Oyagbemi et al. (2020)
SOD activity	Rat, Wistar (M)	Kidney	+	↓	350 ppm	Oral administration (in drinking-water), 7 days	A single dose tested; multiple end-points detected.	Akinrinde et al. (2016)
	Rat, SD (M)	Kidney	+	↓	300 mg/L	Oral administration (in drinking-water), 28 days	A single dose tested; multiple end-points detected.	Abdel-Daim et al. (2020)
CAT activity	Rat, Wistar (M)	Heart	+	↑	350 ppm	Oral administration (in drinking-water), 7 days	A single dose tested; multiple end-points detected.	Akinrinde et al. (2016)
	Rat, SD (M)	Kidney	+ ↓	↓	300 mg/L	Oral administration (in drinking-water), 28 days	A single dose tested; multiple end-points detected.	Abdel-Daim et al. (2020)
MPO activity	Rat, Wistar (M)	Serum	+	↑	150 mg/kg [bw]/day	Intragastric, 8 days, 1×/day	A single dose tested; multiple end-points detected.	Oyagbemi et al. (2020)
GSH level	Rat, SD (M)	Bile	+	↑	250 µmol/kg [bw]	Subcutaneous, 1–72 h, single dose	Time-dependent effect.	Stelzer & Klaassen (1985)

Table S4.14 (continued)

End-point	Species, strain, (sex)	Tissue	Results ^a	Direction of response	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
GSH level (cont.)	Syrian golden hamster, (M or F)	Lung	+	↓	1–10 000 µg/kg [bw]	Intratracheal instillation, 3–48 h, single dose	Dose-dependent effect.	Lewis et al. (1991)
	Rat, Wistar (M)	Kidneys, heart	+	↑	350 ppm	Oral administration (in drinking-water), 7 days	A single dose tested; multiple end-points detected.	Akinrinde et al. (2016)
		Cardiac and renal tissues	+	↑	150 mg/kg [bw]/day	Intragastric, 8 days, 1×/day	A single dose tested; multiple end-points detected.	Oyagbemi et al. (2020)
	Rat, SD (M)	Kidney	+	↑	300 mg/L	Oral administration (in drinking-water), 28 days	A single dose tested; multiple end-points detected.	Abdel-Daim et al. (2020)
GSSG level	Syrian golden Hamsters (M or F)	Lung	+	↑	1–10 000 µg/kg [bw]	Intratracheal instillation, 3–48 h, single dose	Dose-dependent effect.	Lewis et al. (1991)
	Rat, SD (M)	Bile	+	↑	250 µmol/kg [bw]	Subcutaneous, 1–72 h, single dose	Time-dependent effect.	Stelzer & Klaassen (1985)
Nrf2 level	Rat, Wistar (M)	Hippocampus	+	↑	4 mg/kg [bw]/day	Intraperitoneal injection, 20 days, 1×/day	A single dose tested; multiple end-points detected.	Zheng et al. (2019)
HO-1 level	Rat, Wistar (M)	Substantia nigra Hippocampus	+	↑	4 mg/kg [bw]/day	Intraperitoneal injection, 20 days, 1×/day	A single dose tested; multiple end-points detected.	Zheng et al. (2019)
MPO level	Rat, SD (M)	Kidney	+	↑	300 mg/L	Oral administration (in drinking-water), 28 days	A single dose tested; multiple end-points detected.	Abdel-Daim et al. (2020)
<i>Cobalt(II) sulfate heptahydrate (CoSO₄·7H₂O)</i>								
Mn-SOD activity	Rat, SD (M)	Myocardium	+ ↓	↓	40 mg/kg [bw]	Oral administration (in feed), 24 wk	A single dose tested with reasonable sample size.	Clyne et al. (2001)
<i>Cobalt(II) acetate (C₄H₆CoO₄)</i>								
Oxidative DNA damage	Rat, F344/NCr (M + F)	Kidney, liver, and lung	+	↑	50–100 µM/kg [bw]	Intraperitoneal injection, 2–10 days, single dose	Dose-dependent effect.	Kasprzak et al. (1994)

Table S4.14 (continued)

End-point	Species, strain, (sex)	Tissue	Results ^a	Direction of response	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
<i>Ultrafine cobalt metal</i>								
Lipid peroxides	Rat, Wistar (M)	BALF	+	↑	1 mg ultrafine cobalt metallic particles with a mean diameter of 20 nm/rat	Intratracheal instillation		Zhang et al. (1998)
<i>Ultrafine cobalt(II,III) oxide (Co₃O₄)</i>								
Hydroxyl radical generation	Rat, Wistar (M)	BALF	(+)	↑	Co ₃ O ₄ : 125 µg/rat	Intratracheal instillation, 4–18 h, single dose	A single dose tested; limited samples (<i>n</i> = 3).	Dick et al. (2003)
<i>Cobalt-based NPs</i>								
MDA level	Rat, Wistar (M)	Temporal lobe and hippocampus	+	↑	Cobalt metal NPs (size, 96 nm): 2–8 mg/kg [bw]/day	Intraperitoneal injection, 20 days, 1×/day	Dose-dependent effect.	Zheng et al. (2019)
8-OHdG level	Mouse, Gpt delta transgenic mice	Lung	+	↑	85–90% cobalt metal and 10–15% Co ₃ O ₄ NPs: 50 µg/mouse	Intratracheal instillation, 1–28 days, single dose	A single dose tested; different durations tested.	Wan et al. (2017)
NRF2 level	Rat, Wistar (M)	Hippocampus	+	↑	Cobalt metal NPs (size, 96 nm): 2–8 mg/kg [bw]/day	Intraperitoneal injection, 20 days, 1×/day	Dose-dependent effect.	Zheng et al. (2019)
HO-1 level	Mouse, C57BL/6 (M)	Lung	+	↑	CoO NPs (size < 100 nm): 20 µg/mouse	Oropharyngeal aspiration, 40 h, single dose	A single dose tested; combine multiple analysis methods.	Zhang et al. (2012)
	Rat, Wistar (M)	Hippocampus	+	↑	Cobalt metal NPs (size, 96 nm): 2–8 mg/kg [bw]/day	Intraperitoneal injection, 20 days, 1×/day	Dose-dependent effect.	Zheng et al. (2019)

Table S4.14 (continued)

End-point	Species, strain, (sex)	Tissue	Results ^a	Direction of response	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
8-oxo-dG level	Mouse, B6C3F1/N (M) and (F)	Lung	+	↑	Cobalt metal dust (high dose, 10 mg/m ³)	Inhalation, 90 days		Ton et al. (2021)

4-HNE, 4-hydroxynonenal; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; AOPP, advanced oxidation protein products; BALF, bronchoalveolar lavage fluid; bw, body weight; CAT, catalase; Cu/Zn-SOD, copper/zinc superoxide dismutase; F, female; Gpt, guanine phosphoribosyltransferase; GPX, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; GSSG, oxidized glutathione; GST, glutathione S-transferase; HID, highest ineffective dose; HO, haem oxygenase; HO-1, haem oxygenase isoenzyme 1; HO-2, haem oxygenase isoenzyme 2; H₂O₂, hydrogen peroxide; LED, lowest effective dose; M, male; MDA, malondialdehyde; min, minute; Mn-SOD, manganese superoxide dismutase; MPO, myeloperoxidase; NO, nitric oxide; NOX2, NADPH oxidase 2; NPSH, non-protein thiol; Nrf2, nuclear factor E2-related factor 2; PC, protein carbonyl; ppm, parts per million; PSH, protein thiol; ROS, reactive oxygen species; SD, Sprague-Dawley; SOD, superoxide dismutase; TAC, total antioxidant capacity; V_C, vitamin C; wk, week.

^a +, positive; –, negative; (+) or (–), positive or negative in a study of limited quality; ↓, decrease; ↑, increase.

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