Supplementary Information

Emerging investigator series: Metal nanoparticles in the freshwater: transformation, bioavailability and effects on invertebrates
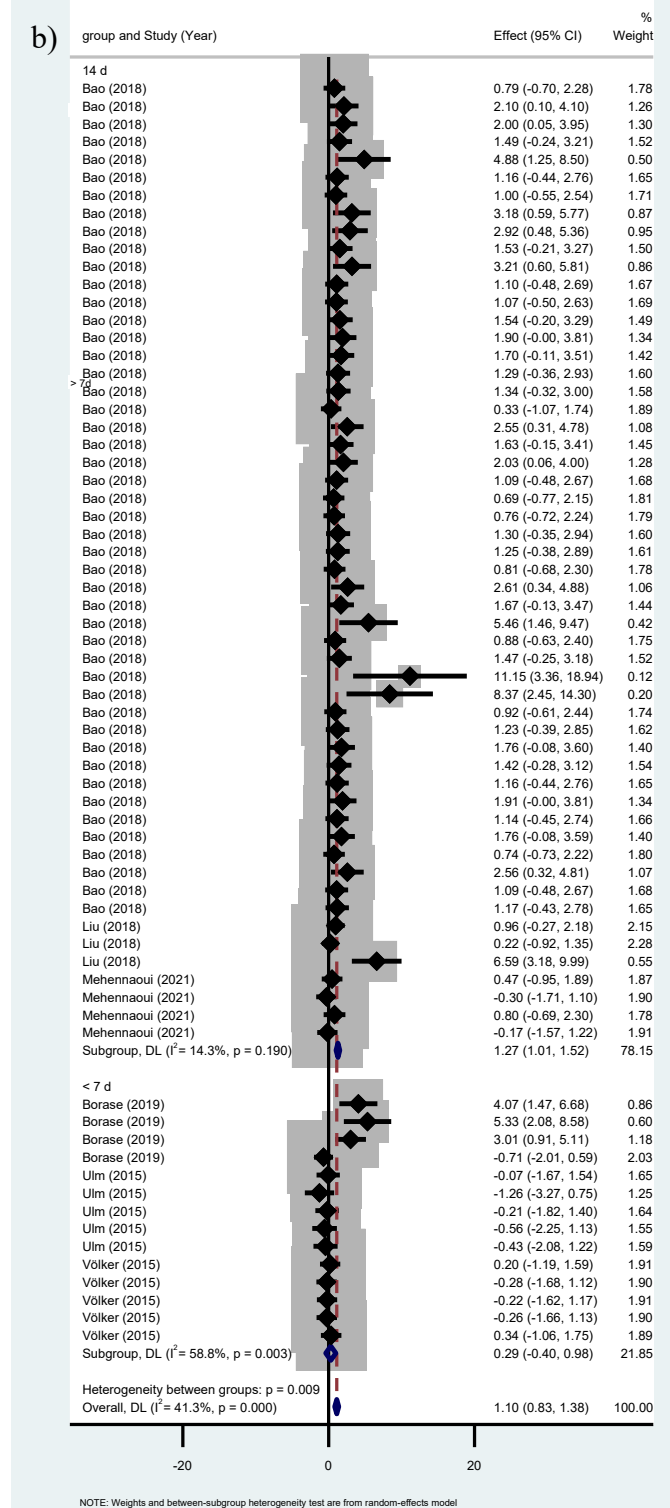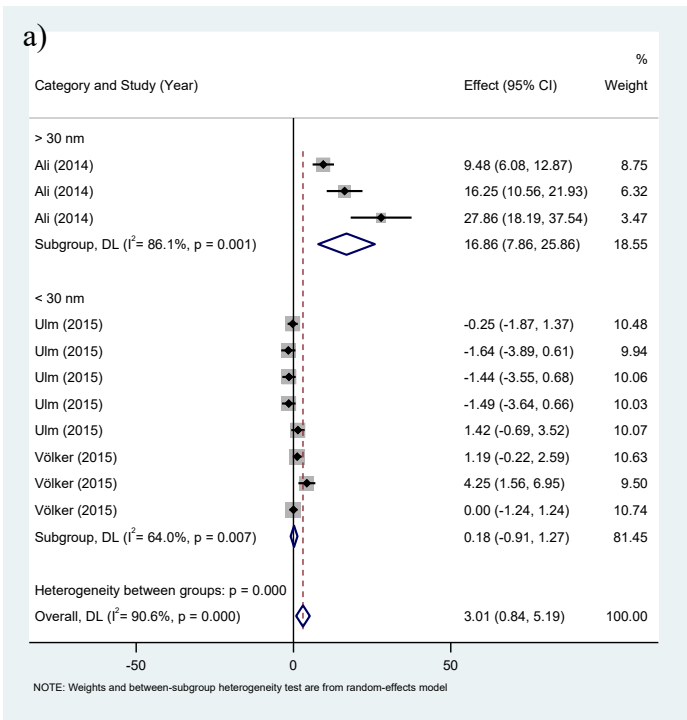
Wang Ting and Wei LIU[*]

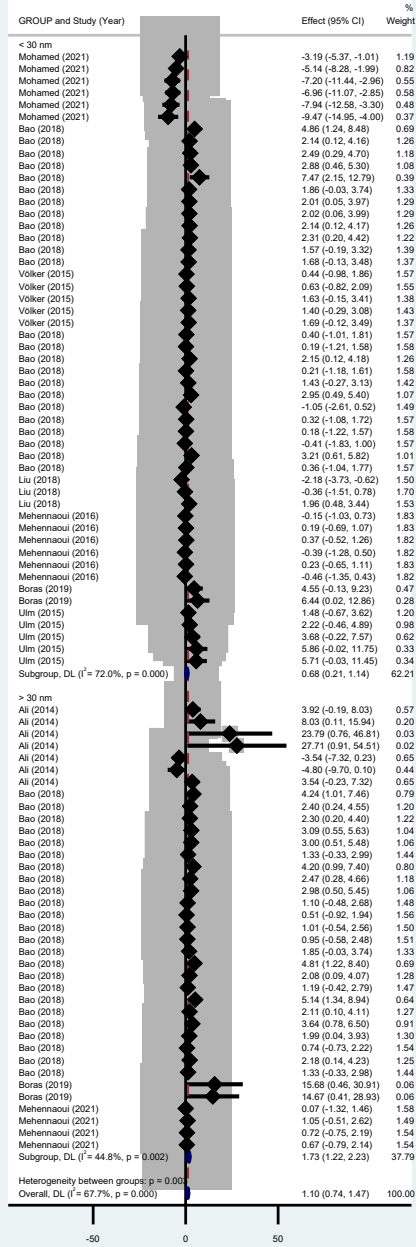University of Geneva, Faculty of Sciences, Earth and Environment Sciences. Switzerland

* Corresponding author; Email: wei.liu@unige.ch

Address: Department F.-A. Forel for Environmental and Aquatic Sciences, Uni Carl Vogt, 66 Blvd Carl-Vogt, CH 1211 Geneva, Switzerland

FIGURE

a)

Category and Study (Year)	Effect (95% CI)	% Weight
> 30 nm		
Ali (2014)	9.48 (6.08, 12.87)	8.75
Ali (2014)	16.25 (10.56, 21.93)	6.32
Ali (2014)	27.86 (18.19, 37.54)	3.47
Subgroup, DL (I^2= 86.1%, p = 0.001)	16.86 (7.86, 25.86)	18.55
< 30 nm		
Ulm (2015)	-0.25 (-1.87, 1.37)	10.48
Ulm (2015)	-1.64 (-3.89, 0.61)	9.94
Ulm (2015)	-1.44 (-3.55, 0.68)	10.06
Ulm (2015)	-1.49 (-3.64, 0.66)	10.03
Ulm (2015)	1.42 (-0.69, 3.52)	10.07
Völker (2015)	1.19 (-0.22, 2.59)	10.63
Völker (2015)	4.25 (1.56, 6.95)	9.50
Völker (2015)	0.00 (-1.24, 1.24)	10.74
Subgroup, DL (I^2= 64.0%, p = 0.007)	0.18 (-0.91, 1.27)	81.45
Heterogeneity between groups: p = 0.000		
Overall, DL (I^2= 90.6%, p = 0.000)	3.01 (0.84, 5.19)	100.00

NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

b)

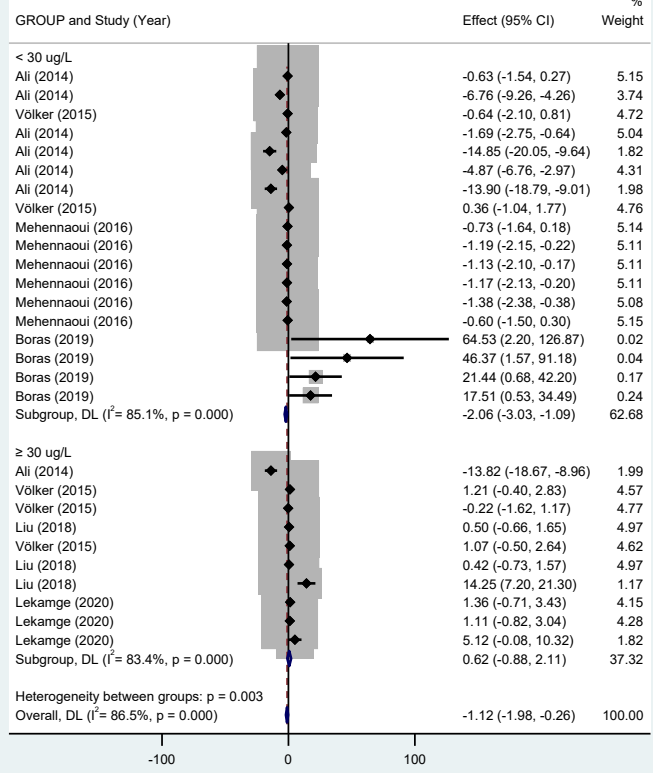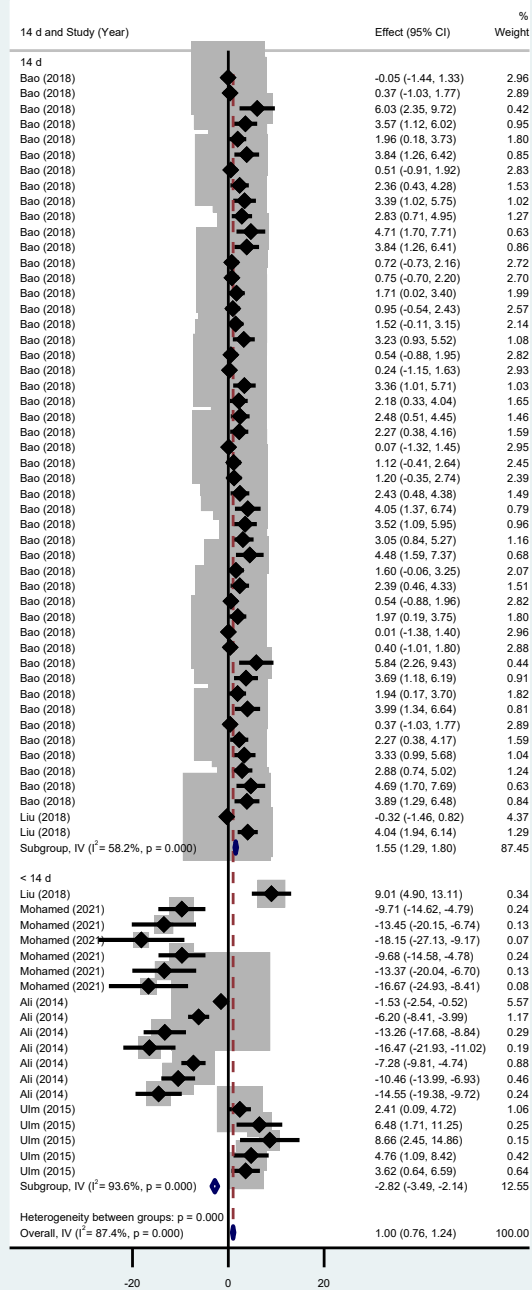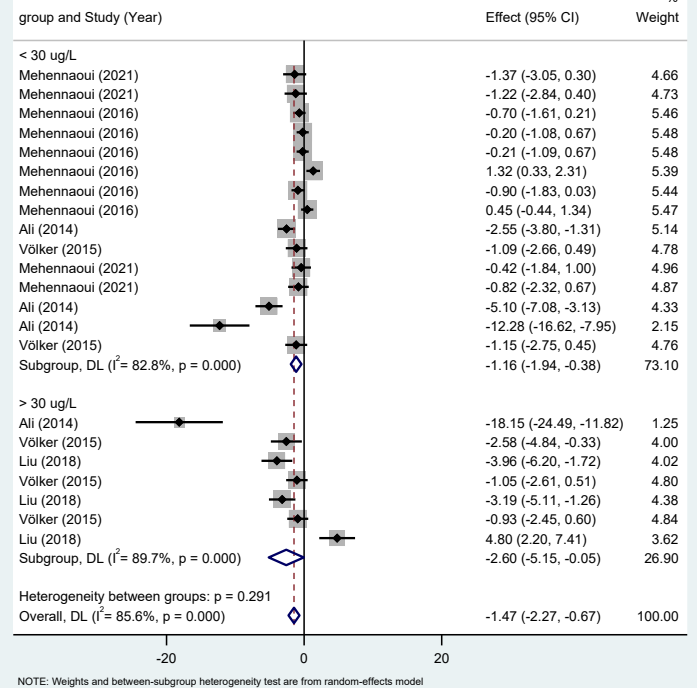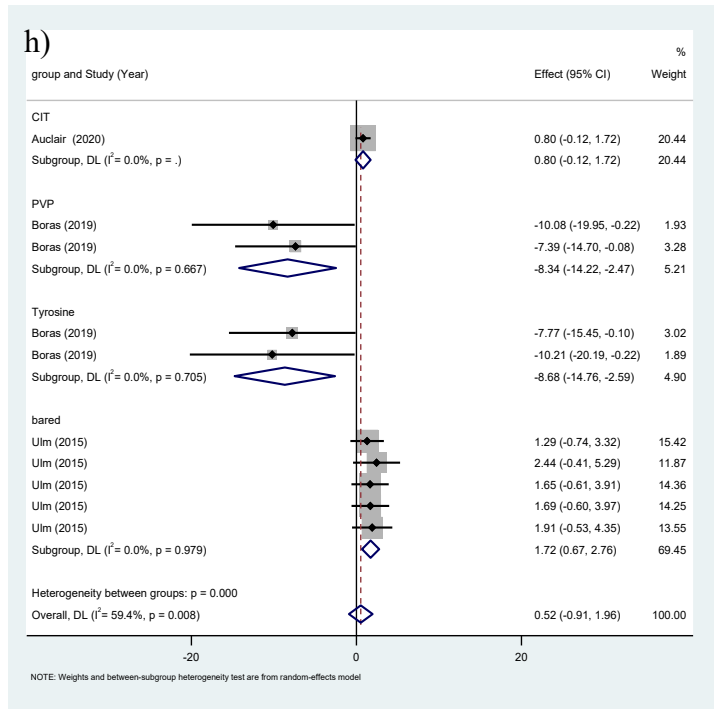| group and Study (Year)	Effect (95% CI)	% Weight
14 d		
Bao (2018)	0.79 (-0.70, 2.28)	1.78
Bao (2018)	2.10 (0.10, 4.10)	1.26
Bao (2018)	2.00 (0.05, 3.95)	1.30
Bao (2018)	1.49 (-0.24, 3.21)	1.52
Bao (2018)	4.88 (1.25, 8.50)	0.50
Bao (2018)	1.16 (-0.44, 2.76)	1.65
Bao (2018)	1.00 (-0.55, 2.54)	1.71
Bao (2018)	3.18 (0.59, 5.77)	0.87
Bao (2018)	2.92 (0.48, 5.36)	0.95
Bao (2018)	1.53 (-0.21, 3.27)	1.50
Bao (2018)	3.21 (0.60, 5.81)	0.86
Bao (2018)	1.10 (-0.48, 2.69)	1.67
Bao (2018)	1.07 (-0.50, 2.63)	1.69
Bao (2018)	1.54 (-0.20, 3.29)	1.49
Bao (2018)	1.90 (-0.00, 3.81)	1.34
Bao (2018)	1.70 (-0.11, 3.51)	1.42
Bao (2018)	1.29 (-0.36, 2.93)	1.60
Bao (2018)	1.34 (-0.32, 3.00)	1.58
Bao (2018)	0.33 (-1.07, 1.74)	1.89
Bao (2018)	2.55 (0.31, 4.78)	1.08
Bao (2018)	1.63 (-0.15, 3.41)	1.45
Bao (2018)	2.03 (0.06, 4.00)	1.28
Bao (2018)	1.09 (-0.48, 2.67)	1.68
Bao (2018)	0.69 (-0.77, 2.15)	1.81
Bao (2018)	0.76 (-0.72, 2.24)	1.79
Bao (2018)	1.30 (-0.35, 2.94)	1.60
Bao (2018)	1.25 (-0.38, 2.89)	1.61
Bao (2018)	0.81 (-0.68, 2.30)	1.78
Bao (2018)	2.61 (0.34, 4.88)	1.06
Bao (2018)	1.67 (-0.13, 3.47)	1.44
Bao (2018)	5.46 (1.46, 9.47)	0.42
Bao (2018)	0.88 (-0.63, 2.40)	1.75
Bao (2018)	1.47 (-0.25, 3.18)	1.52
Bao (2018)	11.15 (3.36, 18.94)	0.12
Bao (2018)	8.37 (2.45, 14.30)	0.20
Bao (2018)	0.92 (-0.61, 2.44)	1.74
Bao (2018)	1.23 (-0.39, 2.85)	1.62
Bao (2018)	1.76 (-0.08, 3.60)	1.40
Bao (2018)	1.42 (-0.28, 3.12)	1.54
Bao (2018)	1.16 (-0.44, 2.76)	1.65
Bao (2018)	1.91 (-0.00, 3.81)	1.34
Bao (2018)	1.14 (-0.45, 2.74)	1.66
Bao (2018)	1.76 (-0.08, 3.59)	1.40
Bao (2018)	0.74 (-0.73, 2.22)	1.80
Bao (2018)	2.56 (0.32, 4.81)	1.07
Bao (2018)	1.09 (-0.48, 2.67)	1.68
Bao (2018)	1.17 (-0.43, 2.78)	1.65
Liu (2018)	0.96 (-0.27, 2.18)	2.15
Liu (2018)	0.22 (-0.92, 1.35)	2.28
Liu (2018)	6.59 (3.18, 9.99)	0.55
Mehennaoui (2021)	0.47 (-0.95, 1.89)	1.87
Mehennaoui (2021)	-0.30 (-1.71, 1.10)	1.90
Mehennaoui (2021)	0.80 (-0.69, 2.30)	1.78
Mehennaoui (2021)	-0.17 (-1.57, 1.22)	1.91
Subgroup, DL (I^2= 14.3%, p = 0.190)	1.27 (1.01, 1.52)	78.15
< 7 d		
Borase (2019)	4.07 (1.47, 6.68)	0.86
Borase (2019)	5.33 (2.08, 8.58)	0.60
Borase (2019)	3.01 (0.91, 5.11)	1.18
Borase (2019)	-0.71 (-2.01, 0.59)	2.03
Ulm (2015)	-0.07 (-1.67, 1.54)	1.65
Ulm (2015)	-1.26 (-3.27, 0.75)	1.25
Ulm (2015)	-0.21 (-1.82, 1.40)	1.64
Ulm (2015)	-0.56 (-2.25, 1.13)	1.55
Ulm (2015)	-0.43 (-2.08, 1.22)	1.59
Völker (2015)	0.20 (-1.19, 1.59)	1.91
Völker (2015)	-0.28 (-1.68, 1.12)	1.90
Völker (2015)	-0.22 (-1.62, 1.17)	1.91
Völker (2015)	-0.26 (-1.66, 1.13)	1.90
Völker (2015)	0.34 (-1.06, 1.75)	1.89
Subgroup, DL (I^2= 58.8%, p = 0.003)	0.29 (-0.40, 0.98)	21.85
Heterogeneity between groups: p = 0.009		
Overall, DL (I^2= 41.3%, p = 0.000)	1.10 (0.83, 1.38)	100.00

NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

c)

GROUP and Study (Year)	Effect (95% CI)	% Weight
< 30 nm		
Mohamed (2021)	-3.19 (-5.37, -1.01)	1.19
Mohamed (2021)	-5.14 (-8.28, -1.99)	0.82
Mohamed (2021)	-7.20 (-11.44, -2.96)	0.55
Mohamed (2021)	-6.96 (-11.07, -2.85)	0.58
Mohamed (2021)	-7.94 (-12.58, -3.30)	0.48
Mohamed (2021)	-9.47 (-14.95, -4.00)	0.37
Bao (2018)	4.86 (1.24, 8.48)	0.69
Bao (2018)	2.14 (0.12, 4.16)	1.26
Bao (2018)	2.49 (0.29, 4.70)	1.18
Bao (2018)	2.88 (0.46, 5.30)	1.08
Bao (2018)	7.47 (2.15, 12.79)	0.39
Bao (2018)	1.86 (-0.03, 3.74)	1.33
Bao (2018)	2.01 (0.05, 3.97)	1.29
Bao (2018)	2.02 (0.06, 3.99)	1.29
Bao (2018)	2.14 (0.12, 4.17)	1.26
Bao (2018)	2.31 (0.20, 4.42)	1.22
Bao (2018)	1.57 (-0.19, 3.32)	1.39
Bao (2018)	1.68 (-0.13, 3.48)	1.37
Völker (2015)	0.44 (-0.98, 1.86)	1.57
Völker (2015)	0.63 (-0.82, 2.09)	1.55
Völker (2015)	1.63 (-0.15, 3.41)	1.38
Völker (2015)	1.40 (-0.29, 3.08)	1.43
Völker (2015)	1.69 (-0.12, 3.49)	1.37
Bao (2018)	0.40 (-1.01, 1.81)	1.57
Bao (2018)	0.19 (-1.21, 1.58)	1.58
Bao (2018)	2.15 (0.12, 4.18)	1.26
Bao (2018)	0.21 (-1.18, 1.61)	1.58
Bao (2018)	1.43 (-0.27, 3.13)	1.42
Bao (2018)	2.95 (0.49, 5.40)	1.07
Bao (2018)	-1.05 (-2.61, 0.52)	1.49
Bao (2018)	0.32 (-1.08, 1.72)	1.57
Bao (2018)	0.18 (-1.22, 1.57)	1.58
Bao (2018)	-0.41 (-1.83, 1.00)	1.57
Bao (2018)	3.21 (0.61, 5.82)	1.01
Bao (2018)	0.36 (-1.04, 1.77)	1.57
Liu (2018)	-2.18 (-3.73, -0.62)	1.50
Liu (2018)	-0.36 (-1.51, 0.78)	1.70
Liu (2018)	1.96 (0.48, 3.44)	1.53
Mehennaoui (2016)	-0.15 (-1.03, 0.73)	1.83
Mehennaoui (2016)	0.19 (-0.69, 1.07)	1.83
Mehennaoui (2016)	0.37 (-0.52, 1.26)	1.82
Mehennaoui (2016)	-0.39 (-1.28, 0.50)	1.82
Mehennaoui (2016)	0.23 (-0.65, 1.11)	1.83
Mehennaoui (2016)	-0.46 (-1.35, 0.43)	1.82
Boras (2019)	4.55 (-0.13, 9.23)	0.47
Boras (2019)	6.44 (0.02, 12.86)	0.28
Ulm (2015)	1.48 (-0.67, 3.62)	1.20
Ulm (2015)	2.22 (-0.46, 4.89)	0.98
Ulm (2015)	3.68 (-0.22, 7.57)	0.62
Ulm (2015)	5.86 (-0.02, 11.75)	0.33
Ulm (2015)	5.71 (-0.03, 11.45)	0.34
Subgroup, DL (I^2= 72.0%, p = 0.000)	0.68 (0.21, 1.14)	62.21
> 30 nm		
Ali (2014)	3.92 (-0.19, 8.03)	0.57
Ali (2014)	8.03 (0.11, 15.94)	0.20
Ali (2014)	23.79 (0.76, 46.81)	0.03
Ali (2014)	27.71 (0.91, 54.51)	0.02
Ali (2014)	-3.54 (-7.32, 0.23)	0.65
Ali (2014)	-4.80 (-9.70, 0.10)	0.44
Ali (2014)	3.54 (-0.23, 7.32)	0.65
Bao (2018)	4.24 (1.01, 7.46)	0.79
Bao (2018)	2.40 (0.24, 4.55)	1.20
Bao (2018)	2.30 (0.20, 4.40)	1.22
Bao (2018)	3.09 (0.55, 5.63)	1.04
Bao (2018)	3.00 (0.51, 5.48)	1.06
Bao (2018)	1.33 (-0.33, 2.99)	1.44
Bao (2018)	4.20 (0.99, 7.40)	0.80
Bao (2018)	2.47 (0.28, 4.66)	1.18
Bao (2018)	2.98 (0.50, 5.45)	1.06
Bao (2018)	1.10 (-0.48, 2.68)	1.48
Bao (2018)	0.51 (-0.92, 1.94)	1.56
Bao (2018)	1.01 (-0.54, 2.56)	1.50
Bao (2018)	0.95 (-0.58, 2.48)	1.51
Bao (2018)	1.85 (-0.03, 3.74)	1.33
Bao (2018)	4.81 (1.22, 8.40)	0.69
Bao (2018)	2.08 (0.09, 4.07)	1.28
Bao (2018)	1.19 (-0.42, 2.79)	1.47
Bao (2018)	5.14 (1.34, 8.94)	0.64
Bao (2018)	2.11 (0.10, 4.11)	1.27
Bao (2018)	3.64 (0.78, 6.50)	0.91
Bao (2018)	1.99 (0.04, 3.93)	1.30
Bao (2018)	0.74 (-0.73, 2.22)	1.54
Bao (2018)	2.18 (0.14, 4.23)	1.25
Bao (2018)	1.33 (-0.33, 2.98)	1.44
Boras (2019)	15.68 (0.46, 30.91)	0.06
Boras (2019)	14.67 (0.41, 28.93)	0.06
Mehennaoui (2021)	0.07 (-1.32, 1.46)	1.58
Mehennaoui (2021)	1.05 (-0.51, 2.62)	1.49
Mehennaoui (2021)	0.72 (-0.75, 2.19)	1.54
Mehennaoui (2021)	0.67 (-0.79, 2.14)	1.54
Subgroup, DL (I^2= 44.8%, p = 0.002)	1.73 (1.22, 2.23)	37.79
Heterogeneity between groups: p = 0.00?		
Overall, DL (I^2= 67.7%, p = 0.000)	1.10 (0.74, 1.47)	100.00

-50   0   50

NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

d)

GROUP and Study (Year)	Effect (95% CI)	% Weight
< 30 ug/L		
Ali (2014)	-0.63 (-1.54, 0.27)	5.15
Ali (2014)	-6.76 (-9.26, -4.26)	3.74
Völker (2015)	-0.64 (-2.10, 0.81)	4.72
Ali (2014)	-1.69 (-2.75, -0.64)	5.04
Ali (2014)	-14.85 (-20.05, -9.64)	1.82
Ali (2014)	-4.87 (-6.76, -2.97)	4.31
Ali (2014)	-13.90 (-18.79, -9.01)	1.98
Völker (2015)	0.36 (-1.04, 1.77)	4.76
Mehennaoui (2016)	-0.73 (-1.64, 0.18)	5.14
Mehennaoui (2016)	-1.19 (-2.15, -0.22)	5.11
Mehennaoui (2016)	-1.13 (-2.10, -0.17)	5.11
Mehennaoui (2016)	-1.17 (-2.13, -0.20)	5.11
Mehennaoui (2016)	-1.38 (-2.38, -0.38)	5.08
Mehennaoui (2016)	-0.60 (-1.50, 0.30)	5.15
Boras (2019)	64.53 (2.20, 126.87)	0.02
Boras (2019)	46.37 (1.57, 91.18)	0.04
Boras (2019)	21.44 (0.68, 42.20)	0.17
Boras (2019)	17.51 (0.53, 34.49)	0.24
Subgroup, DL (I^2= 85.1%, p = 0.000)	-2.06 (-3.03, -1.09)	62.68
≥ 30 ug/L		
Ali (2014)	-13.82 (-18.67, -8.96)	1.99
Völker (2015)	1.21 (-0.40, 2.83)	4.57
Völker (2015)	-0.22 (-1.62, 1.17)	4.77
Liu (2018)	0.50 (-0.66, 1.65)	4.97
Völker (2015)	1.07 (-0.50, 2.64)	4.62
Liu (2018)	0.42 (-0.73, 1.57)	4.97
Liu (2018)	14.25 (7.20, 21.30)	1.17
Lekamge (2020)	1.36 (-0.71, 3.43)	4.15
Lekamge (2020)	1.11 (-0.82, 3.04)	4.28
Lekamge (2020)	5.12 (-0.08, 10.32)	1.82
Subgroup, DL (I^2= 83.4%, p = 0.000)	0.62 (-0.88, 2.11)	37.32
Heterogeneity between groups: p = 0.003		
Overall, DL (I^2= 86.5%, p = 0.000)	-1.12 (-1.98, -0.26)	100.00

-100   0   100

NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

e)

14 d and Study (Year)	Effect (95% CI)	% Weight
14 d		
Bao (2018)	-0.05 (-1.44, 1.33)	2.96
Bao (2018)	0.37 (-1.03, 1.77)	2.89
Bao (2018)	6.03 (2.35, 9.72)	0.42
Bao (2018)	3.57 (1.12, 6.02)	0.95
Bao (2018)	1.96 (0.18, 3.73)	1.80
Bao (2018)	3.84 (1.26, 6.42)	0.85
Bao (2018)	0.51 (-0.91, 1.92)	2.83
Bao (2018)	2.36 (0.43, 4.28)	1.53
Bao (2018)	3.39 (1.02, 5.75)	1.02
Bao (2018)	2.83 (0.71, 4.95)	1.27
Bao (2018)	4.71 (1.70, 7.71)	0.63
Bao (2018)	3.84 (1.26, 6.41)	0.86
Bao (2018)	0.72 (-0.73, 2.16)	2.72
Bao (2018)	0.75 (-0.70, 2.20)	2.70
Bao (2018)	1.71 (0.02, 3.40)	1.99
Bao (2018)	0.95 (-0.54, 2.43)	2.57
Bao (2018)	1.52 (-0.11, 3.15)	2.14
Bao (2018)	3.23 (0.93, 5.52)	1.08
Bao (2018)	0.54 (-0.88, 1.95)	2.82
Bao (2018)	0.24 (-1.15, 1.63)	2.93
Bao (2018)	3.36 (1.01, 5.71)	1.03
Bao (2018)	2.18 (0.33, 4.04)	1.65
Bao (2018)	2.48 (0.51, 4.45)	1.46
Bao (2018)	2.27 (0.38, 4.16)	1.59
Bao (2018)	0.07 (-1.32, 1.45)	2.95
Bao (2018)	1.12 (-0.41, 2.64)	2.45
Bao (2018)	1.20 (-0.35, 2.74)	2.39
Bao (2018)	2.43 (0.48, 4.38)	1.49
Bao (2018)	4.05 (1.37, 6.74)	0.79
Bao (2018)	3.52 (1.09, 5.95)	0.96
Bao (2018)	3.05 (0.84, 5.27)	1.16
Bao (2018)	4.48 (1.59, 7.37)	0.68
Bao (2018)	1.60 (-0.06, 3.25)	2.07
Bao (2018)	2.39 (0.46, 4.33)	1.51
Bao (2018)	0.54 (-0.88, 1.96)	2.82
Bao (2018)	1.97 (0.19, 3.75)	1.80
Bao (2018)	0.01 (-1.38, 1.40)	2.96
Bao (2018)	0.40 (-1.01, 1.80)	2.88
Bao (2018)	5.84 (2.26, 9.43)	0.44
Bao (2018)	3.69 (1.18, 6.19)	0.91
Bao (2018)	1.94 (0.17, 3.70)	1.82
Bao (2018)	3.99 (1.34, 6.64)	0.81
Bao (2018)	0.37 (-1.03, 1.77)	2.89
Bao (2018)	2.27 (0.38, 4.17)	1.59
Bao (2018)	3.33 (0.99, 5.68)	1.04
Bao (2018)	2.88 (0.74, 5.02)	1.24
Bao (2018)	4.69 (1.70, 7.69)	0.63
Bao (2018)	3.89 (1.29, 6.48)	0.84
Liu (2018)	-0.32 (-1.46, 0.82)	4.37
Liu (2018)	4.04 (1.94, 6.14)	1.29
Subgroup, IV (I^2= 58.2%, p = 0.000)	1.55 (1.29, 1.80)	87.45
< 14 d		
Liu (2018)	9.01 (4.90, 13.11)	0.34
Mohamed (2021)	-9.71 (-14.62, -4.79)	0.24
Mohamed (2021)	-13.45 (-20.15, -6.74)	0.13
Mohamed (2021)	-18.15 (-27.13, -9.17)	0.07
Mohamed (2021)	-9.68 (-14.58, -4.78)	0.24
Mohamed (2021)	-13.37 (-20.04, -6.70)	0.13
Mohamed (2021)	-16.67 (-24.93, -8.41)	0.08
Ali (2014)	-1.53 (-2.54, -0.52)	5.57
Ali (2014)	-6.20 (-8.41, -3.99)	1.17
Ali (2014)	-13.26 (-17.68, -8.84)	0.29
Ali (2014)	-16.47 (-21.93, -11.02)	0.19
Ali (2014)	-7.28 (-9.81, -4.74)	0.88
Ali (2014)	-10.46 (-13.99, -6.93)	0.46
Ali (2014)	-14.55 (-19.38, -9.72)	0.24
Ulm (2015)	2.41 (0.09, 4.72)	1.06
Ulm (2015)	6.48 (1.71, 11.25)	0.25
Ulm (2015)	8.66 (2.45, 14.86)	0.15
Ulm (2015)	4.76 (1.09, 8.42)	0.42
Ulm (2015)	3.62 (0.64, 6.59)	0.64
Subgroup, IV (I^2= 93.6%, p = 0.000)	-2.82 (-3.49, -2.14)	12.55
Heterogeneity between groups: p = 0.000		
Overall, IV (I^2= 87.4%, p = 0.000)	1.00 (0.76, 1.24)	100.00

-20   0   20

f)

group and Study (Year)	Effect (95% CI)	% Weight
< 30 ug/L		
Mehennaoui (2021)	-1.37 (-3.05, 0.30)	4.66
Mehennaoui (2021)	-1.22 (-2.84, 0.40)	4.73
Mehennaoui (2016)	-0.70 (-1.61, 0.21)	5.46
Mehennaoui (2016)	-0.20 (-1.08, 0.67)	5.48
Mehennaoui (2016)	-0.21 (-1.09, 0.67)	5.48
Mehennaoui (2016)	1.32 (0.33, 2.31)	5.39
Mehennaoui (2016)	-0.90 (-1.83, 0.03)	5.44
Mehennaoui (2016)	0.45 (-0.44, 1.34)	5.47
Ali (2014)	-2.55 (-3.80, -1.31)	5.14
Völker (2015)	-1.09 (-2.66, 0.49)	4.78
Mehennaoui (2021)	-0.42 (-1.84, 1.00)	4.96
Mehennaoui (2021)	-0.82 (-2.32, 0.67)	4.87
Ali (2014)	-5.10 (-7.08, -3.13)	4.33
Ali (2014)	-12.28 (-16.62, -7.95)	2.15
Völker (2015)	-1.15 (-2.75, 0.45)	4.76
Subgroup, DL (I^2= 82.8%, p = 0.000)	-1.16 (-1.94, -0.38)	73.10
> 30 ug/L		
Ali (2014)	-18.15 (-24.49, -11.82)	1.25
Völker (2015)	-2.58 (-4.84, -0.33)	4.00
Liu (2018)	-3.96 (-6.20, -1.72)	4.02
Völker (2015)	-1.05 (-2.61, 0.51)	4.80
Liu (2018)	-3.19 (-5.11, -1.26)	4.38
Völker (2015)	-0.93 (-2.45, 0.60)	4.84
Liu (2018)	4.80 (2.20, 7.41)	3.62
Subgroup, DL (I^2= 89.7%, p = 0.000)	-2.60 (-5.15, -0.05)	26.90
Heterogeneity between groups: p = 0.291		
Overall, DL (I^2= 85.6%, p = 0.000)	-1.47 (-2.27, -0.67)	100.00

-20   0   20

NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

Fig.S1 Meta-analysis of a) ROS; b) SOD; c) CAT; d) GST; e) GSH; f) GPx; g) LPO; and h) AChE in freshwater invertebrates. The dot represents the effect size of each study. The line through the dot represents 95%CI of the effect size. The square represents the weight, $W*i$. The bigger the square, the bigger the weight. The broken line represents the effect size and the horizontal length of the diamond, the 95%CI of the effect size for all studies combined.
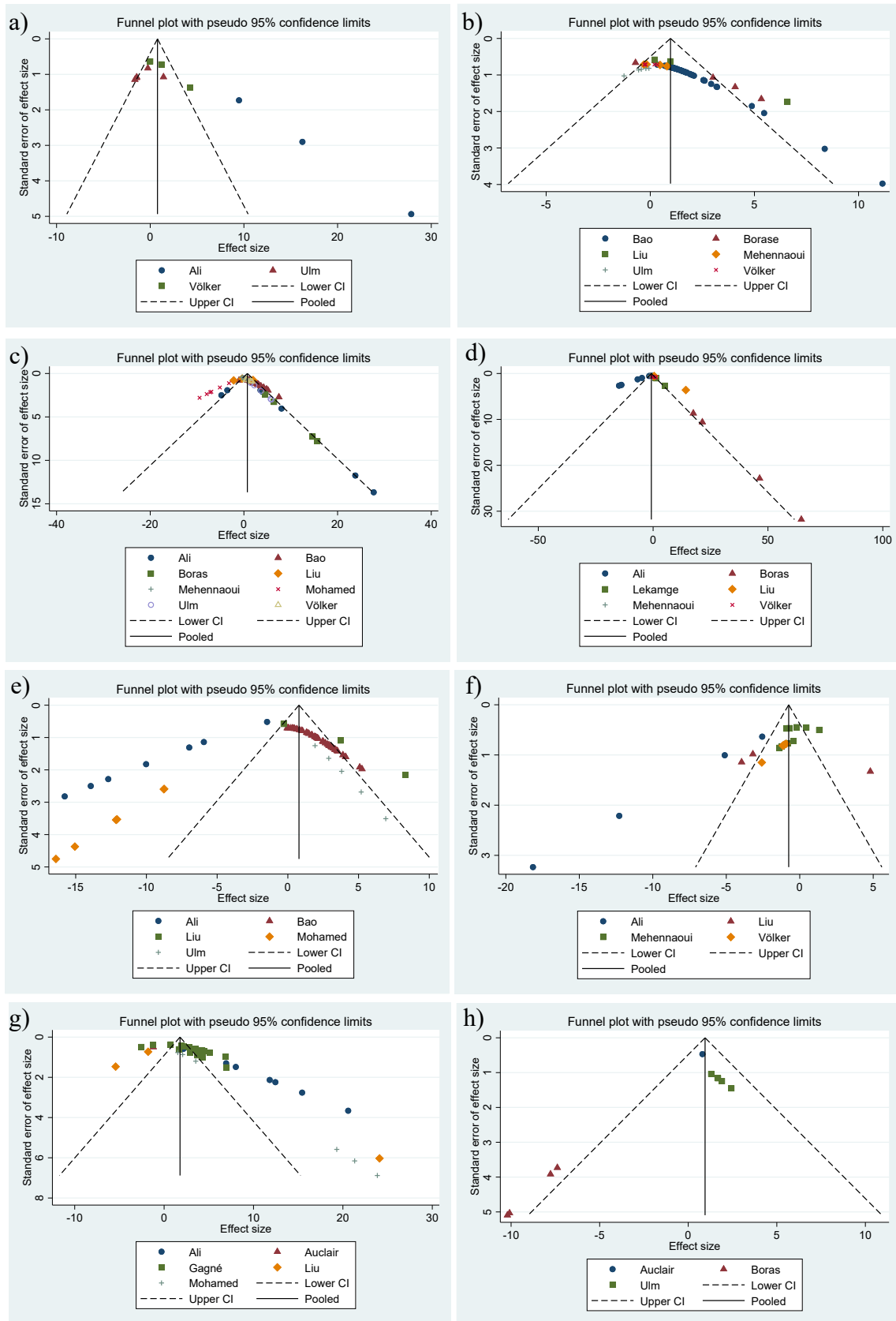
Fig.S2 Funnel plots of a) ROS; b) SOD; c) CAT; d) GST; e) GSH; f) GPx; g) LPO; and h)

AChE for experimental studies included in meta-analysis.
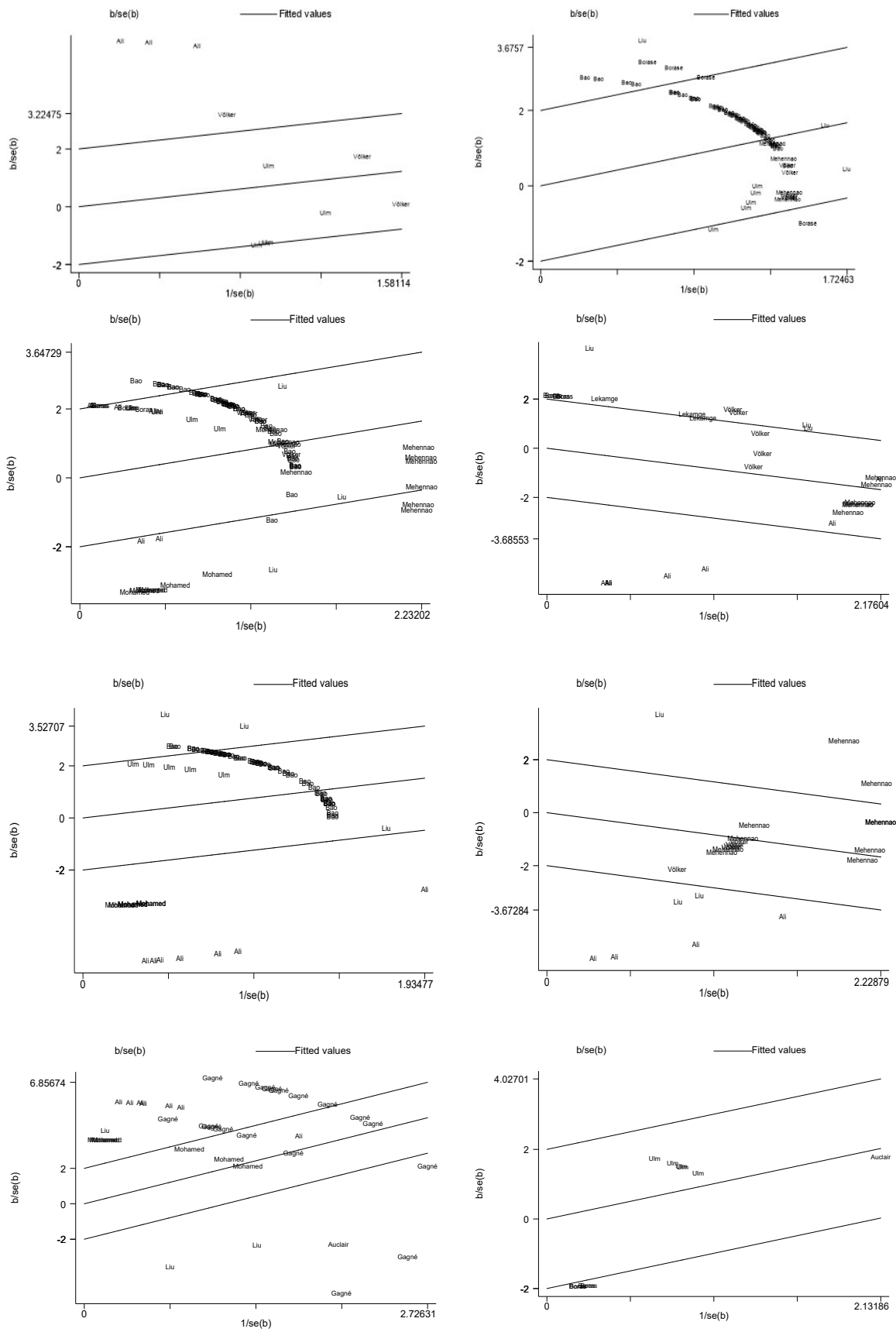
Fig.S3. Sensitivity analysis of a) ROS; b) SOD; c) CAT; d) GST; e) GSH; f) GPx; g) LPO; and h) AChE for experimental studies included in meta-analysis.

Table S1. Meta aggression analyses according to different factors for biomarkers.

Heterogeneous factor	p (95% Conf. Interval)			
	ROS	SOD	CAT	GST
Size	0.002 (0.409~1.382)	0.428 (-0.007~0.017)	0.040 (0.001~0.043)	0.113 (-0.549~0.062)
Conc.	0.965 (-0.219~0.228)	0.028 (0.000~00.004)	0.398 (-0.003~0.001)	0.031 (0.001~0.015)
Time	0.009 (0.068~0.364)	0.000 (0.002~0.006)	0.078 (-0.000~0.007)	0.235 (-0.005~0.020)
Coating*	/	0.169 (-0.65~0.117)	0.874 (-0.821~0.700)	0.044 (0.042~03.030)
Size*Conc.	0.436 (-0.009~0.019)	0.022 (0.000~0.000)	0.611 (-0.000~0.000)	0.036 (0.000~0.001)
Size*Time	0.002 (0.003~0.009)	0.127 (-7.09e-06~0.000)	0.137 (-0.000~0.000)	0.332 (-0.000~0.001)
Size*Coating	/	0.494 (-0.010~0.005)	0.911 (-0.010~0.011)	0.015 (0.022~0.190)
Size*Conc.*Time*Coating	0.004 (0.000~0.000)	0.035 (7.47e-09~1.98e-07)	0.803 (-6.41e-08~8.25e-08)	0.028 (4.93e-08~8.06e-07)
	GPx	GSH	LPO	AChE
Size	0.155 (-0.559~0.097)	0.214 (-0.018~0.080)	0.403 (-0.116~0.048)	0.450 (-0.370~0.180)
Conc.	0.125 (-0.001~.0069)	0.583 (-0.004~0.006)	0.061 (-0.000~0.0160)	0.519 (-0.150~0.269)
Time	0.644 (-0.010~0.016)	0.000 (0.017~0.036)	0.886 (-0.027~0.031)	0.698 (-0.176~0.250)
Coating	0.525 (-1.22~2.31)	0.243 (-2.39~9.26)	0.261 (-4.11~01.152)	0.048 (-3.61~.020)
Size*Conc.	0.131 (-0.000~0.000)	0.096 (-0.000~0.000)	0.113 (-0.000~0.006)	0.631 (-0.003~0.005)
Size*Time	0.721 (-0.000~0.000)	0.015 (0.000~0.000)	0.494 (-0.001~0.001)	0.929 (-0.003~0.003)
Size*Coating	0.726 (-0.032~0.045)	0.243 (-2.39~9.26)	0.366 (-0.050~0.019)	0.151 (-0.070~0.013)
Size*Conc.*Time*Coating	0.123 (-4.77e-08~3.73e-07)	0.064 (-1.57e-08 5.23e-07)	0.136 (-1.16e-07~8.13e-07)	0.687 (-0.000~0.000)

Table S2. Subgroup analyses of the meta-analysis according to different factors for biomarkers

Subgroup measurement		df	p	I^2 (%)	SMD [95% Conf. Interval]	df	p	I^2 (%)	SMD [95% Conf. Interval]
	ROS					**CAT**			
Size	< 30 nm	7.00	0.01	64.00	0.182 (-0.91~1.27)	50	< 0.001	72.0	0.68 (0.21~1.14)
	> 30 nm	2.00	< 0.001	86.10	16.86 (7.86~25)	36	< 0.001	44.8	1.73 (1.22~2.23)
	Overall	10.00	< 0.001	90.60	3.01 (0.84~5.19)	87	< 0.001	77.8	1.10 (0.74~1.47)
	GST					**GPx**			
Conc.	< 30 ug/L	17	< 0.001	85.1	-2.06 (-3.03~-1.09)	14	< 0.001	82.8	-1.16 (-1.94~-0.38)
	≥ 30 ug/L	9	< 0.001	83.4	0.62 (-0.88~2.11)	6	< 0.001	89.7	-2.60 (-5.15~-0.05)
	Overall	27	< 0.001	86.5	-1.12 (-1.98~-0.26)	21	< 0.001	85.6	-1.47 (-2.27~-0.67)
	LPO								
		23	< 0.001	93.9	4.10 (2.98~5.22)				
	≥ 30 ug/L	10	< 0.001	92.1	4.58 (1.82~7.35)				
	Overall	34	< 0.001	93.7	3.99 (2.94~5.04)				
	SOD					**GSH**			
Time	< 14 d	13	0.003	58.8	0.29 (-0.40~0.98)	17	< 0.001	93.6	-2.82 (-3.49~-2.14)
	14 d	53	0.19	14.3	1.27 (1.01~1.52)	50	< 0.001	58.2	1.55 (1.29~1.80)
	Overall	67	< 0.001	41.3	1.10 (0.83~1.38)	68	< 0.001	87.4	1.00 (0.76~1.24)
	AChE								
Coating	CIT	0		0	0.80 (-0.12~1.72)				
	PVP	1	0.667	0	-8.34 (-14.22~-2.47)				
	Tyrosine	1	0.705	0	-8.68 (-14.76~-2.59)				
	bared	4	0.979	0	1.72 (0.67~2.76)				
	Overall	9	0.008	59.4	0.52 (-0.91~1.96)				