# Probabilistic risk assessment of zinc oxide nanoparticles from consumer products to health of adult populations

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**Supporting Information**

**Table S1** In vivo toxicity data of n-ZnO

| No. | n-ZnO | Laboratory animal | Dose (mg/(kg•bw)) | Exposure method | Depuration time | Effect | Ref |
|---|---|---|---|---|---|---|---|
| 1 | n-ZnO (mean size 80 nm) | Swiss albino male mice Mus musculus (8-12 weeks old, weighing 25-30 g) were obtained from departmental animal house | 25,50, 100 | Oral | 0, 24, and 45h | 100 mg/kg induce toxicity in bone marrow and liver cells. | [1] |
| 2 | n-ZnO (20 and 120 nm) | CD-ICR mice 20–22 g (8 weeks old) female and male | 1,000, 2,000, 3,000, 4,000, 5,000 | Oral | 14 days | The 120 nm ZnO-treated mice had dose–effect pathological damages in the stomach, liver, heart and spleen, whereas 20 nm ZnO caused negative dose–effect damage to the liver, spleen, and pancreas. | [2] |
| 3 | n-ZnO (mean size 32 nm) | Male Swiss albino mice $20 \pm 2$ g ($\sim$6 weeks old) were obtained from the Indian Institute of Toxicology Research (Lucknow, India) | 50, 300 | Oral | 14 days | Sub-acute oral exposure to n-ZnO in mice led to an accumulation of nanoparticles in the liver causing oxidative stress, mediated DNA damage, and apoptosis. | [3] |
| 4 | n-ZnO | Sprague–Dawley (SD) rats (11/sex/group) were obtained from OrientBio Ltd (Seongnam, Korea) | 67.1, 134.2, 268.4, 536.8 | Oral | 13 weeks | These results indicate that the bio-persistence of n-ZnO after ingestion is key to their toxicity; the no observed adverse effect level (NOAEL) of n-ZnO was found to be 268.4 mg/kg day for both sexes. | [4] |
| 5 | n-ZnO (mean size $44.17 \pm 6.35$ nm) | Nine-week-old nulliparous female and over 12-week-old male Sprague Dawley rats were purchased from Orient Bio (Seoul, Korea). | 5, 10, 20 | Intravenous Injection | 14 days | Based on the data, the lowest observed adverse effect level of injection exposure in dams was suggested to be 5 mg/kg, which was based on the liver damage indicated by ALP increase and the NOAEL was 10 mg/kg in fetal developmental toxicity. | [5] |

| | | | | | | |
|---|---|---|---|---|---|---|
| 6 | n-ZnO (20 nm) | Sprague Dawley rats, 8 to 9 weeks old were procured from breeding facilities of International Institute of Biotechnology and Toxicology (IIBAT) | 5, 50, 300, 1,000, 2,000 | Oral | 14 days | We concluded that nano-size zinc oxide exhibited toxicity at lower doses; thus, future nanotoxicology research needs to be focused on importance of dose metrics rather than following the conventional methods while conducting in vivo experiments. [6] |
| 7 | n-ZnO (20 nm) | Sprague Dawley rats aged 6 weeks old and weighing 150-210 g were obtained from an inhouse animal facility | 250, 500, 1,000 | Oral | 90 days | This study demonstrated that there was no observed adverse effect of n-ZnO up to 1000 mg/kg body weight when they were applied dermally. [7] |
| 8 | n-ZnO (27.5 ± 4.1 nm) | Ten pregnant female Sprague–Dawley rats (SD rats) were purchased from the Experimental Animal Center of Nanchang University (Nanchang, China) | 68, 203, 610 | Oral | 28 days | We infer that n–ZnO affected bone growth in young rats directly or indirectly by altering IGF-1 levels. Overall, the results indicate that n-ZnO promoted osteoclast activity and increased bone loss through the OPG/RANK/RANKL/IGF-1 pathway. [8] |
| 9 | n-ZnO (50 nm) | Three-week-old healthy Kunming mice, 12 ± 2 g, were supplied by the Experimental Animal Center of Zhengzhou University, 12 male and 12 female mice in each group | 40, 80, 160, 320 | Oral | 90 days | The main cause for oxidative stress in vivo induced by n-ZnO could be hydroxyl free radical. The lowest observed adverse effect level (LOAEL) was 40 mg/(kg·bw), and the livers, kidneys, lungs, pancreas, and gastrointestinal tracts were the target organs. [9] |
| 10 | n-ZnO | Seven-week-old Sprague Dawley male rats (200–225 g) were purchased from Orient Bio (Gyeonggi-do, Korea). | 3, 30 | Oral | 7 days | n-ZnO were distributed mainly in the liver, kidneys, lung, and spleen, but not the thymus, brain, and testes. In rats injected with 30 mg/kg n-ZnO, mitotic Fig.s in hepatocytes were significantly increased and multifocal acute injuries with dark brown pigments were noted in the lungs, whereas no significant damage was observed in rats treated [10] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | orally with the same dosage. | |
| 11 | n-ZnO (20–30 nm) | Twelve female rats (Wistar), aged 6–8 weeks were purchased from animal house of veterinary department of Urmia University | 333.33 | Oral gavage | 1 day | Glomeruli segmentation, hydropic degeneration in epithelial cells, necrosis of the epithelial cells in tubules, and swelling in the epithelial cells of proximal tubules were found in all kidney tissues, which demonstrated that n-ZnO had severe toxicological effects on the kidneys. Serous inflammation, severe hyperemia in the alveoli, and oedema were observed as pathological findings in the lungs, which suggested that the lung was the third target tissue of the n-ZnO. | [11] |
| 12 | n-ZnO (20 ± 10 nm) | Adult male Wistar rats (140–160 g) were purchased from Beijing Vitalriver Experimental Animal Technology Co. Ltd (Beijing, China) | 2.5 | Oral | 3 days | n-ZnO was administered at a dose 2.5 mg/kg body weight, twice daily for 3 days. The levels of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total protein (TP), creatine kinase (CK), and lactate dehydrogenase (LDH) in both nanoparticle-exposed groups were significantly decreased compared to the unexposed controls. Histopathological examination showed that both types of nanoparticles caused severe damage in the liver and lung tissues. | [12] |
| 13 | n-ZnO (< 100 nm) | Fifty Wistar albino rats (170–200 g) were used. The rats were obtained from the Experimental Animal Care Center, College of Pharmacy, King Saud University. | 600 | Oral | 5 days | n-ZnO -induced nephrotoxicity was confirmed by the elevation in serum inflammatory markers including: interleukin-6(IL-6) and C-reactive protein (CRP). Moreover, immunoglobulin (IGg), vascular endothelium growth factor (VEGF), and nitric oxide (NO) were significantly increased in rat serum. Severe congestion was also observed in renal interstitium. These effects were dose dependent. | [13] |

**Table S2** Toxicity data screening based on Klimisch evaluation system *in vivo* experimental system

| Rank | Identification of experimental materials | Characteristics of experimental system | Experimental design description | Record of experimental results | Feasibility of experimental design and documentation | Total score | Ref |
|------|------|------|------|------|------|------|------|
| 1 | 4 | 5 | 6 | 3 | 2 | 19 | [6] |
| 2 | 2 | 5 | 6 | 3 | 2 | 17 | [4] |
| 3 | 2 | 4 | 5 | 3 | 2 | 16 | [9] |
| 4 | 2 | 3 | 6 | 3 | 2 | 16 | [2] |
| 5 | 3 | 4 | 4 | 3 | 1 | 15 | [7] |
| 6 | 4 | 3 | 4 | 1 | 1 | 14 | [8] |
| 7 | 2 | 4 | 5 | 1 | 1 | 13 | [3] |
| 8 | 2 | 3 | 4 | 2 | 1 | 13 | [5] |
| 9 | 2 | 3 | 5 | 1 | 2 | 13 | [14] |
| 10 | 2 | 4 | 4 | 1 | 1 | 12 | [11] |
| 11 | 3 | 3 | 3 | 2 | 1 | 12 | [10] |
| 12 | 2 | 3 | 4 | 1 | 2 | 12 | [12] |
| 13 | 1 | 3 | 3 | 2 | 1 | 11 | [13] |

**Table S3** The evaluation results of toxicity data based on the selected 13 papers. An expert panel scored each of the identified studies on a scale from 1 to 5, with 5 denoting the highest quality.

| Rank | Adequacy | Reliability | Relevance | Quantity | Toxicological significance | Average score | Ref |
|---|---|---|---|---|---|---|---|
| 1 | 4 | 5 | 5 | 5 | 4 | 4.6 | [6] |
| 2 | 4 | 4 | 4 | 5 | 5 | 4.4 | [4] |
| 3 | 4 | 4 | 4 | 4 | 4 | 4 | [9] |
| 4 | 4 | 3 | 4 | 3 | 4 | 3.6 | [7] |
| 5 | 4 | 3 | 4 | 3 | 3 | 3.4 | [2] |
| 6 | 3 | 2 | 4 | 3 | 4 | 3.2 | [8] |
| 7 | 3 | 3 | 3 | 2 | 4 | 3 | [10] |
| 8 | 3 | 2 | 4 | 2 | 2 | 2.6 | [5] |
| 9 | 2 | 3 | 2 | 2 | 2 | 2.2 | [3] |
| 10 | 2 | 2 | 2 | 2 | 2 | 2 | [11] |
| 11 | 2 | 3 | 1 | 1 | 2 | 1.8 | [14] |
| 12 | 3 | 2 | 2 | 1 | 1 | 1.8 | [12] |
| 13 | 2 | 2 | 1 | 1 | 1 | 1.4 | [13] |

**Table S4** Dose response assessments of selected studies with sufficient quality by BMDS software

| Particle size (nm) | Difference in sex | Variable | Values | Ref |
|---|---|---|---|---|
| 20 | Females | BMD | 202.04 | [6] |
| | | AIC | 316.97 | |
| | | Test 4 P-value | 0.03979 | |
| | | D.O.F. | 2 | |
| | Males | BMD | 43.52 | |
| | | AIC | 314.01 | |
| | | Test 4 P-value | 0.02567 | |
| | | D.O.F. | 2 | |
| 40 | Males | BMD | / | [4] |
| | | AIC | 327.93 | |
| | | Test 4 P-value | 0.1554 | |
| | | D.O.F. | 2 | |
| | Females | BMD | 241.36 | |
| | | AIC | 369.0575496 | |
| | | Test 4 P-value | 0.001621043 | |
| | | D.O.F. | 2 | |
| 50 | / | BMD | 179.83 | [9] |
| | | AIC | 400.59 | |
| | | Test 4 P-value | <0.0001 | |
| | | D.O.F. | 2 | |
| 29 | Females | BMD | / | [7] |
| | | AIC | 353.2631513 | |
| | | Test 4 P-value | 0.009850812 | |
| | | D.O.F. | 1 | |
| | Males | BMD | / | |
| | | AIC | 353.2631513 | |

| | | | | |
|---|---|---|---|---|
| | | Test 4 P-value | 0.009850812 | |
| | | D.O.F. | 1 | |
| 20 | / | BMD | 442.24 | |
| | | AIC | 280.11 | |
| | | Test 4 P-value | 0.04022 | |
| | | D.O.F. | 2 | [2] |
| 120 | / | BMD | 4237.28 | |
| | | AIC | 315.93 | |
| | | Test 4 P-value | 0.07292 | |
| | | D.O.F. | 3 | |
| 27.5 | / | / | / | [8] |
| 50 | / | BMD | 179.83 | |
| | | AIC | 400.60 | [10] |
| | | Test 4 P-value | <0.0001 | |
| | | D.O.F. | 2 | |

**Table S5** Physicochemical properties of n-ZnO in hazard assessment

| Physicochemical properties | Values |
|---|---|
| Average size [a] | 20 nm |
| Size using SEM | 63 nm |
| Size in distilled water [b] | 224.7 nm |
| Polydispersity index | 0.305 |
| Surface area [c] | 50 m$^2$/g |
| Zeta potential [d] | 30.9 mV |

SEM: Scanning Electron Microscopy; [a] data from the manufacturer; [b] Dynamic Light Scattering (DLS). [c] BET (Brunauer, Emmett, Teller) analysis; [d] Zeta-sizer

**Methods for determining and characterizing physicochemical properties of n-ZnO**

ZnO nanoparticles (Stock No. 5810HT) were purchased from Nanostructured and Amorphous Materials, Inc. USA. The ZnO (Product No. ZO385) was purchased from Sigma Aldrich, USA. The size of nano-size ZnO was determined with scanning electron microscopy (SEM), at Anna University, SEM produces images by rastering a primary electron beam across the sample surface while detecting secondary or backscattered electrons, which are emitted from the surface. Therefore, the images obtained in an SEM provide a 3D quality and greater resolution. In this study, Hitachi S-520 SEM was used at an accelerating voltage of 10,000 V after depositing the samples onto aluminum stubs with double-sided carbon adhesive tape. Photon correlation spectroscopy or DLS is an analytical technique capable of measuring the size of very small particles, at low sample concentrations. Measurement of particle size of nano ZnO in solution was determined with DLS on a Malvern Zetasizer nanoseries (Nano ZS) with Malvern application software version 6.20. This instrument can measure particle sizes ranging from 0.6 nm to 6 mm using noninvasive back scatter (NIBS) technology and DLS. The Malvern Zetasizer can also provide zeta potential measurements in aqueous and nonaqueous dispersions using M3-phase analysis light scattering (PALS) technology. Zeta potential is defined as the accumulation of charge around the surface of a particle in solution and gives an indication of the stability of the colloidal system.

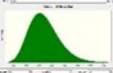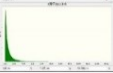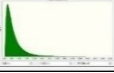## 2. Assumptions and forecasts of Crystal ball runs

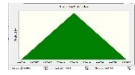*Run preferences*: Number of trials run: 100,000, Confidence level: 95.00%
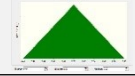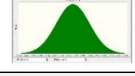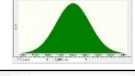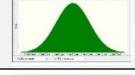
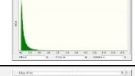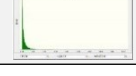*Run statistics*: **Female**: Through oral exposure, Total running time (sec): 0.92, Trials/second (average): 108,603, Random numbers per sec: 1,194,631; Through dermal exposure, Total running time (sec): 1.06, Trials/second (average): 94,230, Random numbers per sec: 942,302;
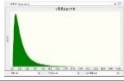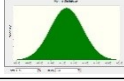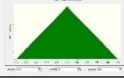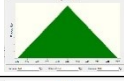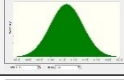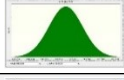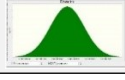
**Male**: Through oral exposure, Total running time (sec): 1.05, Trials/second (average): 95,362, Random numbers per sec: 858,257; Through dermal exposure, Total running time (sec): 1.48, Trials/second (average): 67,414, Random numbers per sec: 539,316;

*Crystal Ball*: Assumptions, 14; Forecasts, 3 (female); Assumptions, 12; Forecasts, 3 (male)

**Table S6** The assumption of variables for the human health risk assessment (HHRA) of n-ZnO for males and females

| Object | Variable | Minimum | GM | Maximum | GSD | Distribution | Diagram |
|---|---|---|---|---|---|---|---|
| Females | $CED_{animal}$ | / | 202 | / | 19.00 | Normal |  |
| | $AF_1$ | / | 5.40 | / | 1.20 | Logistic-Normal |  |
| | $AF_2$ | / | 1.00 | / | 2.00 | Logistic-Normal |  |
| | $AF_{intra}$ | / | 0.60 | / | 1.60 | Logistic-Normal |  |
| | $AF_{subacute\text{-}chronic}$ | / | 4.10 | / | 4.40 | Logistic-Normal |  |

| Parameter | | | | | Distribution | |
|---|---|---|---|---|---|---|
| *Absorption factor* | 0.0001 | 0.0003 | 0.0005 | / | Triangular |  |
| $U_1$ | 0.005 | 0.006 | 0.007 | / | Triangular |  |
| $U_2$ *(oral)* | 0.10 | 0.20 | 0.30 | / | Triangular |  |
| $U_2$ *(dermal)* | 0.0045 | 0.005 | 0.0055 | / | Triangular |  |
| $U_3$ | 0.40 | 0.50 | 0.60 | / | Triangular |  |
| $U_4$ | 0.40 | 0.50 | 0.60 | | Triangular |  |
| $V_1$ | / | 0.903 | / | 0.2027 | Normal |  |
| $V_2$ | / | 0.225 | / | 0.0225 | Normal |  |
| $V_3$ | / | 0.00262 | / | 0.000027 | Normal |  |
| $V_4$ | / | 0.000000054 | / | 0.00000000236 | Normal |  |
| $CED_{animal}$ | / | 43.5 | / | 2.00 | Normal |  |
| $AF_1$ | / | 5.7 | / | 1.20 | Logistic-Normal |  |
| $AF_2$ | / | 1.00 | / | 2.00 | Logistic-Normal |  |
| $AF_{intra}$ | / | 0.60 | / | 1.60 | Logistic-Normal |  |

**Males**

| | | | | | | |
|---|---|---|---|---|---|---|
| $AF_{subacute\text{-}chronic}$ | / | 4.10 | / | 4.40 | Logistic-Normal |  |
| Absorption factor | 0.0001 | 0.0003 | 0.0005 | / | Triangular |  |
| $U_1$ | 0.004 | 0.0.005 | 0.0.006 | / | Triangular |  |
| $U_3$ | 0.40 | 0.50 | 0.60 | / | Triangular |  |
| $U_4$ | 0.40 | 0.50 | 0.60 | / | Triangular |  |
| $V_1$ | / | 0.1272 | / | 0.0287 | Normal |  |
| $V_3$ | / | 0.00229 | / | 0.0000236 | Normal |  |
| $V_4$ | / | 0.0000000472 | / | 0.00000000207 | Normal |  |

$CED_{animal}$ is represented as critical effect dose for toxicity testing, mg/(kg·d); $AF_1$: represent the corrects for body weight differences between test animal and human; $AF_2$: estimates the substance-specific physiologically based toxicokinetic and toxicodynamic (PBTK/TD) differences between test animal and human; $AF_{intra}$ :represent the variability within the human population; $AF_{subacute\text{-}chronic}$: represent the sub-acute-chronic assessment factor; $U_{1, 2, ...n}$ is the uncertainty of n-ZnO nanomaterial intake in relation to product 1, 2, …, n.; $V_{1, 2, ...n}$ is the variability of the assessed nanomaterial n-ZnO in relation to linked to product 1, 2, …, n

**Table S7** The forecast of *ICED*, *IEXP*, and *IMoE* for females through oral exposure

| Forecast: *ICED* | | | | Forecast: *IEXP* | | | | Forecast: *IMoE* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Statistics | Forecast values | Percentiles | Forecast values | Statistics | Forecast values | Percentiles | Forecast values | Statistics | Forecast values | Percentiles | Forecast values |
| Trials | 100,000 | 0% | 0.002152 | Trials | 100,000 | 0% | 0.01528 | Trials | 100,000 | 0% | 0.04319 |
| Base Case | 0.01000 | 10% | 9.04 | Base Case | 0.5000 | 10% | 0.03295 | Base Case | 0.3000 | 10% | 208.3 |
| Mean | 1,366 | 20% | 24.59 | Mean | 0.5000 | 20% | 0.03718 | Mean | 31,148 | 20% | 540.8 |
| Median | 143.6. | 30% | 48.06 | Median | 0.5000 | 30% | 0.04041 | Median | 3,182.6 | 30% | 1,056 |
| Mode | --- | 40% | 84.52 | Mode | --- | 40% | 0.043289 | Mode | --- | 40% | 1,860 |
| Standard Deviation | 10,116 | 50% | 143.7 | Standard Deviation | 0.1000 | 50% | 0.04599 | Standard Deviation | $2.312\times10^5$ | 50% | 3,182 |
| Variance | $1.023\times10^8$ | 60% | 245.0 | Variance | 0.00 | 60% | 0.04874 | Variance | $5.343\times10^{10}$ | 60% | 5,431 |
| Skewness | 67.15 | 70% | 440.4 | Skewness | 0.1983 | 70% | 0.05167 | Skewness | 55.77 | 70% | 9,798 |
| Kurtosis | 8,869 | 80% | 857.2 | Kurtosis | 2.683 | 80% | 0.05519 | Kurtosis | 5,840 | 80% | 19,229 |
| Coeff. of Variation | 7.400 | 90% | 2,201 | Coeff. of Variation | 0.2218 | 90% | 0.05999 | Coeff. of Variation | 7.420 | 90% | 49,440 |
| Minimum | 0.00 | 100% | $1.705\times10^6$ | Minimum | 0.02000 | 100% | 0.08955 | Minimum | 0.0400 | 100% | $3.409\times10^7$ |
| Maximum | $1.705\times10^6$ | / | / | Maximum | 0.08955 | / | / | Maximum | $3.409\times10^7$ | / | / |

| Mean Std. Error | 31.99 | / | / | Mean Std. Error | 0.00 | / | / | Mean Std. Error | 730.9 | / | / |

*ICED*: represent as individual human critical effect dose of females, mg/(kg·d); *IEXP*: represent individual margin of exposure of females; *IMoE*:

The individual margin of exposure represents the distance between a person's individual exposure (*IEXP*) and critical effect dose (*ICED*).

**Table S8** The forecast of *ICED*, *IEXP*, and *IMoE* for females through dermal exposure

| Forecast: *ICED* | | | | Forecast: *IEXP* | | | | Forecast: *IMoE* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Statistics | Forecast values | Percentiles | Forecast values | Statistics | Forecast values | Percentiles | Forecast values | Statistics | Forecast values | Percentiles | Forecast values |
| Trials | 100,000 | 0% | 0.00000169 | Trials | 100,000 | 0% | 0.000826 | Trials | 100,000 | 0% | 0.0003147 |
| Base Case | 0.00000416 | 10% | 0.00265745 | Base Case | 0.006543 | 10% | 0.004908 | Base Case | 0.0006359 | 10% | 0.4117 |
| Mean | 0.4388 | 20% | 0.00689135 | Mean | 0.006538 | 20% | 0.005449 | Mean | 70.17 | 20% | 1.066 |
| Median | 0.0420 | 30% | 0.01352931 | Median | 0.006515 | 30% | 0.005843 | Median | 6.581 | 30% | 2.107 |
| Mode | --- | 40% | 0.02422977 | Mode | --- | 40% | 0.006189 | Mode | --- | 40% | 3.767 |
| Standard Deviation | 5.889 | 50% | 0.04204513 | Standard Deviation | 0.001284 | 50% | 0.006515 | Standard Deviation | 953.857 | 50% | 6.580 |
| Variance | 34.68 | 60% | 0.07225491 | Variance | 0.000002 | 60% | 0.006841 | Variance | 909843.423 | 60% | 11.31 |
| Skewness | 131.35 | 70% | 0.12998107 | Skewness | 0.100526 | 70% | 0.007192 | Skewness | 132.749 | 70% | 20.40 |
| Kurtosis | 22587.72 | 80% | 0.25980233 | Kurtosis | 3.020986 | 80% | 0.007616 | Kurtosis | 23722.951 | 80% | 40.78 |
| Coeff. of Variation | 13.42 | 90% | 0.66043842 | Coeff. of Variation | 0.196465 | 90% | 0.008202 | Coeff. of Variation | 13.594 | 90% | 105.0 5 |
| Minimum | 0.00 | 100% | 1197.08557 | Minimum | 0.000826 | 100% | 0.012312 | Minimum | 0.000 | 100% | 202,645 |
| Maximum | 1197.09 | / | / | Maximum | 0.012312 | / | / | Maximum | 202645.998 | / | / |

| Mean Std. Error | 0.0186 | / | / | Mean Std. Error | 0.011486 | / | / | Mean Std. Error | 202645.998 | / | / |

*ICED*: represent as individual human critical effect dose of females, mg/(kg·d); *IEXP*: represent individual margin of exposure of females; *IMoE*: The individual margin of exposure represents the distance between a person's individual exposure (*IEXP*) and critical effect dose (*ICED*).

**Table S9** The forecast of *ICED*, *IEXP*, and *IMoE* for males through oral exposure

| Forecast: *ICED* | | | | Forecast: *IEXP* | | | | Forecast: *IMoE* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Statistics | Forecast values | Percentiles | Forecast values | Statistics | Forecast values | Percentiles | Forecast values | Statistics | Forecast values | Percentiles | Forecast values |
| Trials | 100,000 | 0% | 0.003400 | Trials | 100,000 | 0% | 0.0008977 | Trials | 100,000 | 0% | 3.098 |
| Base Case | 0.002800 | 10% | 1.948 | Base Case | 0.001145 | 10% | 0.001018 | Base Case | 2.471 | 10% | 1,714 |
| Mean | 286.9 | 20% | 4.947 | Mean | 0.001145 | 20% | 0.001060 | Mean | 252,704 | 20% | 4,331 |
| Median | 29.70 | 30% | 9.719 | Median | 0.001145 | 30% | 0.001093 | Median | 25,959 | 30% | 8,492 |
| Mode | --- | 40% | 17.32 | Mode | --- | 40% | 0.001120 | Mode | --- | 40% | 15,161 |
| Standard Deviation | 2,838 | 50% | 29.69 | Standard Deviation | 0.00009437 | 50% | 0.001145 | Standard Deviation | $2.407 \times 10^6$ | 50% | 25,959 |
| Variance | $8.057 \times 10^6$ | 60% | 50.64 | Variance | 0.006501 | 60% | 0.001170 | Variance | $5.791 \times 10^{12}$ | 60% | 44,338 |
| Skewness | 104.1 | 70% | 89.61 | Skewness | 2.422 | 70% | 0.001197 | Skewness | 88.61 | 70% | 78,395 |
| Kurtosis | 16,789 | 80% | 177.5 | Kurtosis | 0.08241 | 80% | 0.001230 | Kurtosis | 12,254 | 80% | 155,824 |
| Coeff. of Variation | 9.890 | 90% | 448.7 | Coeff. of Variation | 0.0008977 | 90% | 0.001273 | Coeff. of Variation | 9.523 | 90% | 394,352 |
| Minimum | 0.0033 | 100% | $5.487 \times 10^5$ | Minimum | 0.001407 | 100% | 0.001407 | Minimum | 3.098 | 100% | $4.182 \times 10^8$ |
| Maximum | $5.487 \times 10^5$ | / | / | Maximum | 0.0005096 | / | / | Maximum | $4.182 \times 10^8$ | / | / |

| Mean Std. Error | 8.975 | / | / | Mean Std. Error | $2.98\times10^{-7}$ | / | / | Mean Std. Error | 7,611 | / | / |
|---|---|---|---|---|---|---|---|---|---|---|---|

*ICED*: represent as individual human critical effect dose of males, mg/(kg·d); *IEXP*: represent individual margin of exposure of males; *IMoE*: The individual margin of exposure represents the distance between a person's individual exposure (*IEXP*) and critical effect dose (*ICED*)

**Table S10** The forecast of *ICED*, *IEXP*, and *IMoE* for males through dermal exposure

| | Forecast: *ICED* | | | | Forecast: *IEXP* | | | | Forecast: *IMoE* | | |
| Statistics | Forecast values | Percentiles | Forecast values | Statistics | Forecast values | Percentiles | Forecast values | Statistics | Forecast values | Percentiles | Forecast values |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Trials | 100,000 | 0% | $2.710\times10^{-7}$ | Trials | 100,000 | 0% | $4.132\times10^{-6}$ | Trials | 100,000 | 0% | 0.0006028 |
| Base Case | $8.490\times10^{-7}$ | 10% | 0.0005451 | Base Case | 0.001272 | 10% | $4.434\times10^{-4}$ | Base Case | $6.674\times10^{-4}$ | 10% | 0.8661 |
| Mean | 0.0836 | 20% | 0.001418 | Mean | 0.000637 | 20% | 0.0005074 | Mean | 141.90 | 20% | 2.254 |
| Median | 0.008517 | 30% | 0.002779 | Median | 0.000633 | 30% | 0.0005539 | Median | 13.79 | 30% | 4.442 |
| Mode | --- | 40% | 0.004956 | Mode | --- | 40% | 0.00059461 | Mode | --- | 40% | 7.971 |
| Standard Deviation | 0.7245 | 50% | 0.008517 | Standard Deviation | 0.0001532 | 50% | 0.0006331 | Standard Deviation | 1,32 | 50% | 13.79 |
| Variance | 0.5248 | 60% | 0.01466 | Variance | $2.346\times10^{-8}$ | 60% | 0.0006715 | Variance | 1,748,866 | 60% | 23.83 |
| Skewness | 82.46 | 70% | 0.02612 | Skewness | 0.1459 | 70% | 0.0007135 | Skewness | 94.57 | 70% | 42.71 |
| Kurtosis | 11,587 | 80% | 0.05231 | Kurtosis | 3.081 | 80% | 0.0007634 | Kurtosis | 14,676 | 80% | 85.62 |
| Coeff. of Variation | 8.663 | 90% | 0.1350 | Coeff. of Variation | 0.2406 | 90% | 0.0008349 | Coeff. of Variation | 9.32 | 90% | 222.7 |
| Minimum | $2.710\times10^{-7}$ | 100% | 129.0 | Minimum | $4.132\times10^{-6}$ | 100% | 0.001368 | Minimum | 0.0006028 | 100% | 250,634 |
| Maximum | 129.04 | / | / | Maximum | 0.001368 | / | / | Maximum | 250,634 | / | / |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mean Error | Std. | 0.002291 | / | / | Mean Error | Std. | $4.843\times10^{-7}$ | / | / | Mean Error | Std. | 4.182 | / | / |

*ICED*: represent as individual human critical effect dose of males, mg/(kg·d); *IEXP*: represent individual margin of exposure of males; *IMoE*: The individual margin of exposure represents the distance between a person's individual exposure (*IEXP*) and critical effect dose (*ICED*)

**Table S11** The fitting model of the cumulative probability of *IMoE*

| Mode | Sigmodal-logistic model | | | |
|---|---|---|---|---|
| Equation | $y = a/(1 + \exp(-k*(x-xc)))$ | | | |
| Name | Female (oral) | Female (dermal) | Male (oral) | Male (dermal) |
| $a$ | 99.76867 ± 0.59185 | 99.7558 ± 0.53842 | 99.93271 ± 0.59942 | 99.75857 ± 0.51656 |
| $x_c$ | 3.50391 ± 0.0104 | 0.81225 ± 0.00965 | 4.41442 ± 0.01051 | 1.13557 ± 0.00923 |
| $k$ | 1.83144 ± 0.02592 | 1.79123 ± 0.01774 | 1.82058 ± 0.02638 | 1.79784 ± 0.01711 |
| Reduced Chi-Sqr | 0.44622 | 0.38371 | 0.45174 | 0.35223 |
| $R^2$ (COD) | 0.99968 | 0.99959 | 0.99969 | 0.99962 |
| Adj $R^2$ | 0.99964 | 0.99955 | 0.99964 | 0.99959 |
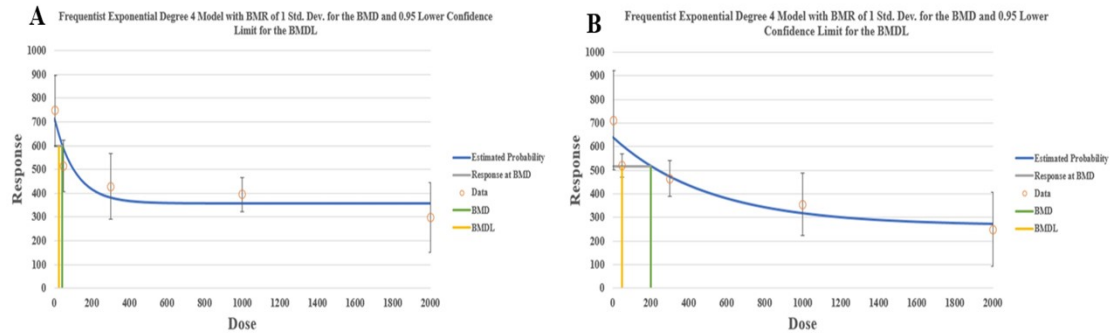
**Fig. S1** The frequentist exponential Degree 4 model of BMR for males (A) and females (B)
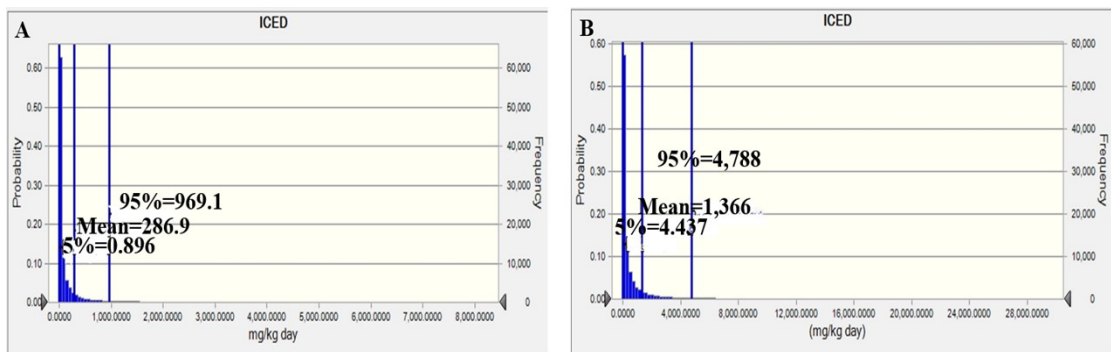


**Fig. S2** Probability distribution of individual human critical effect dose (*ICED*) for males (A) and females (B) through oral exposure
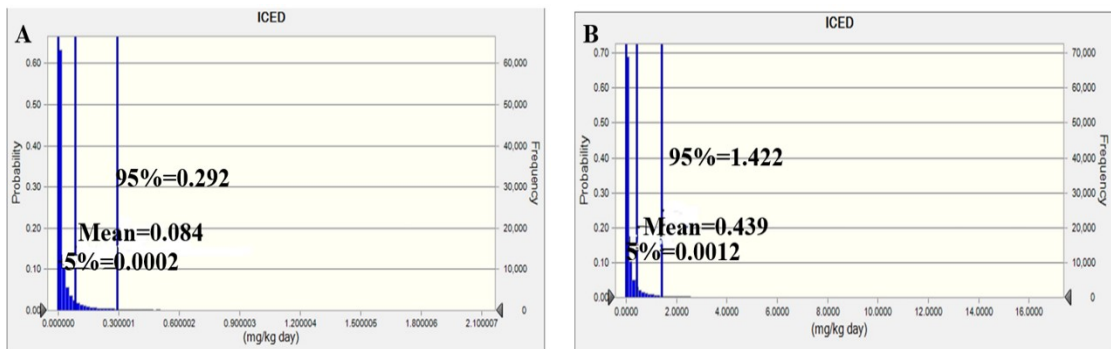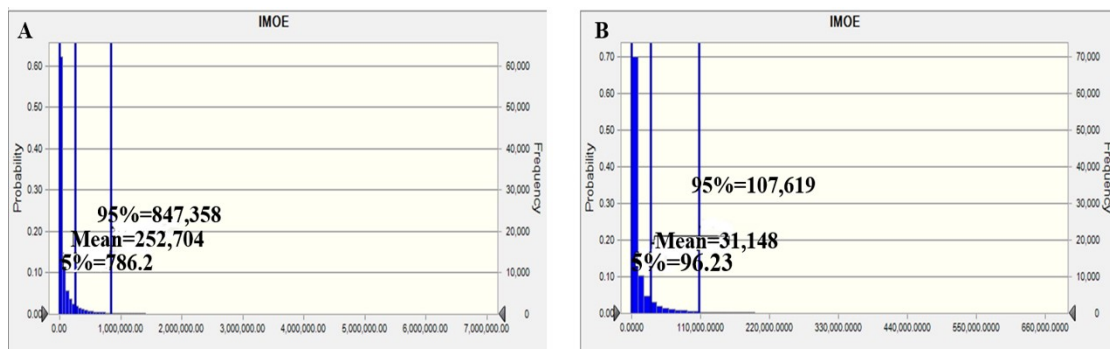


**Fig. S3** Probability distribution of individual human critical effect dose (*ICED*) for males (A) and females (B) through dermal exposure
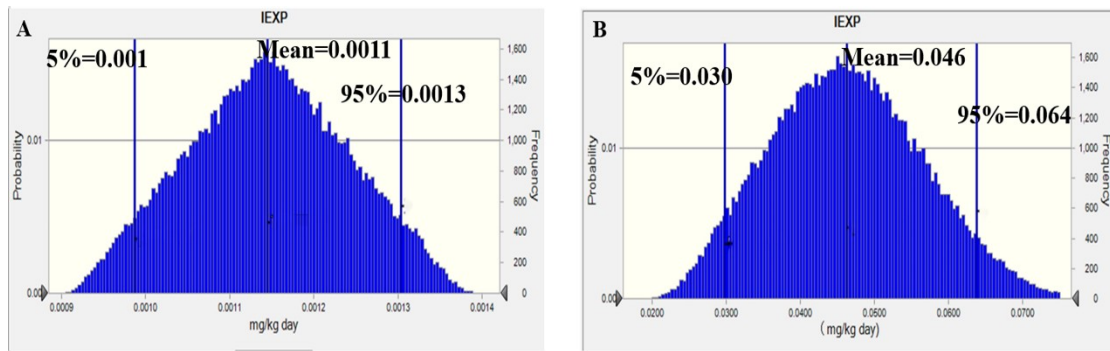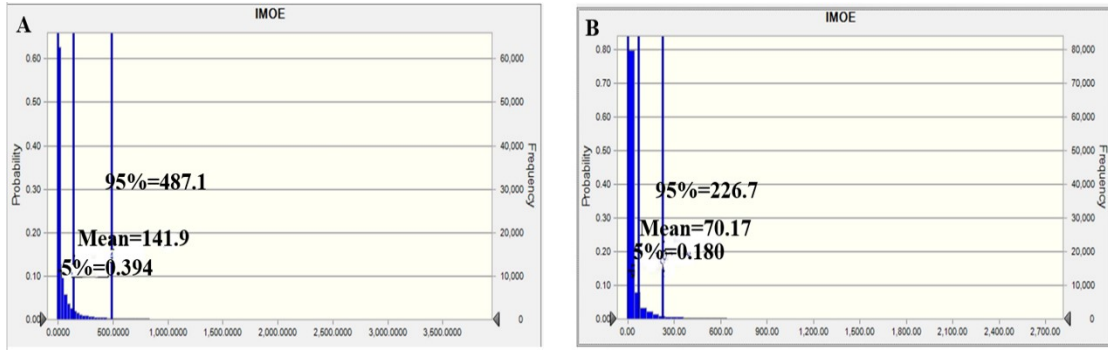
**Fig. S4** Probability distribution of individual exposure level values for (*IEXP*) for males (A) and females (B) through oral exposure
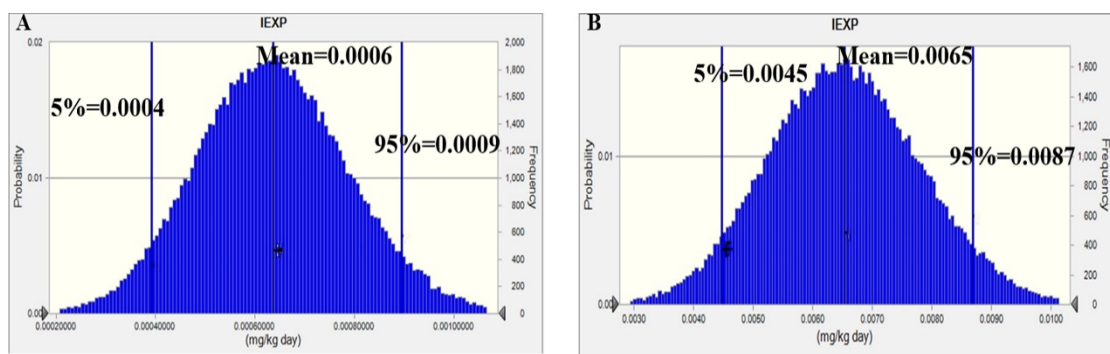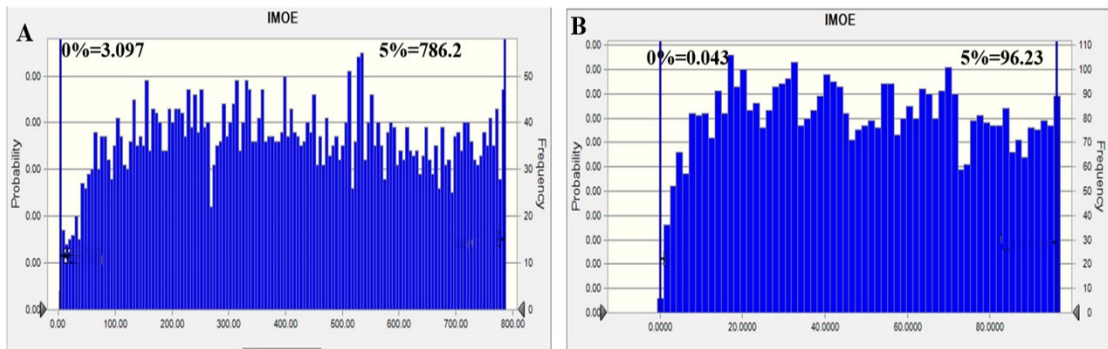


**Fig. S5** Probability distribution of individual exposure level values for (*IEXP*) for males (A) and females (B) through dermal exposure
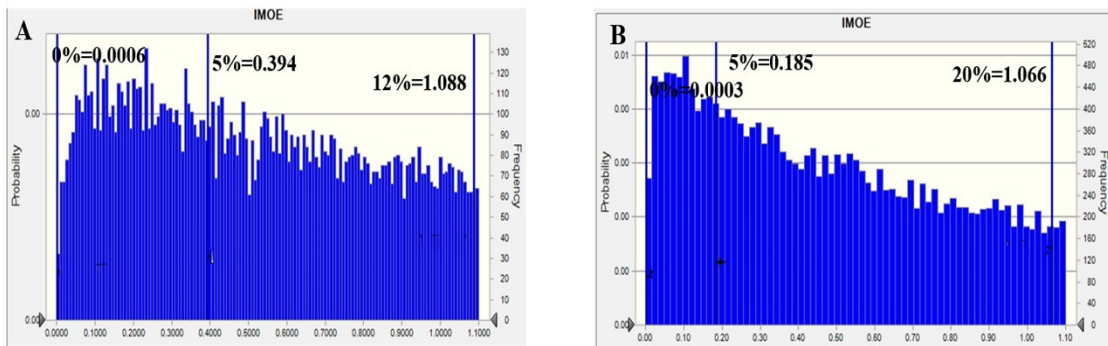


**Fig. S6** Probability distribution of individual exposure margin (*IMoE*) for males (A) and females (B) through oral exposure

**Fig. S7** Probability distribution of individual exposure margin (*IMoE*) for males (A) and females (B) through dermal exposure



**Fig. S8** Initial section of the probability distribution of individual exposure margin (*IMoE*) for males (A) and females (B), where the minimum *IMoE* is lower than 1 in females through oral exposure (0-5% interval)



**Fig. S9** Initial section of the probability distribution of individual exposure margin (*IMoE*) for males (A) and females (B), where the minimum *IMoE* is lower than 1 in both sexes through dermal exposure (0-11.45% interval for males and 0-18.87% interval for females)
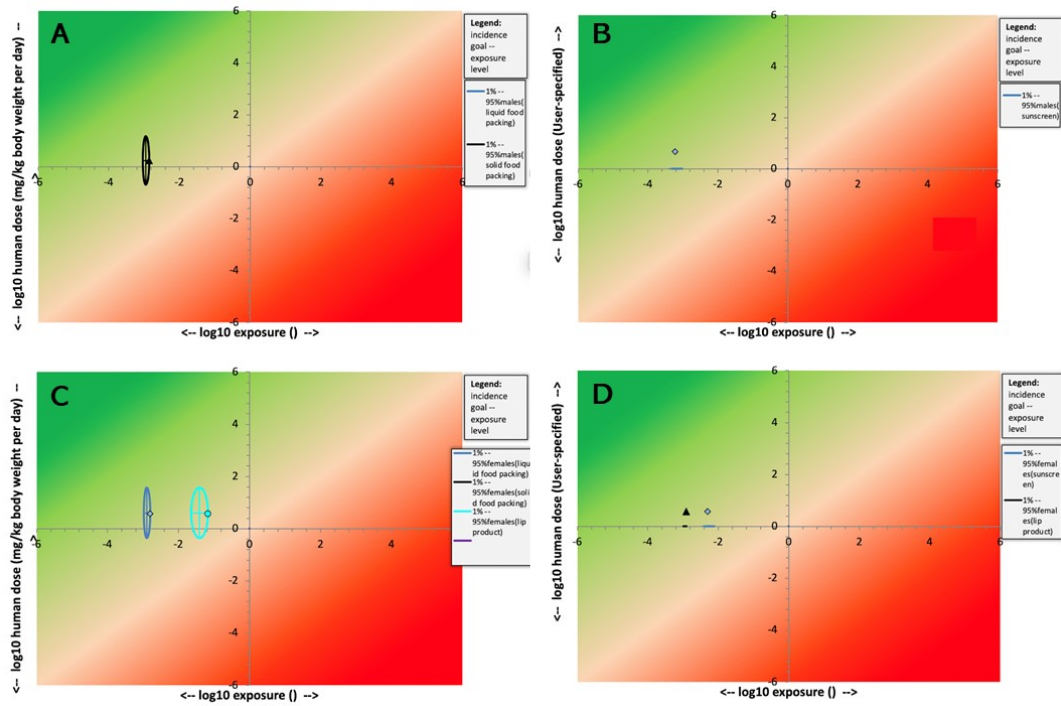
**Fig. S10** Probabilistic risk assessment of n-ZnO by the APROBA-plus tool, oral exposure of adult males (A), oral exposure of adult females (B), dermal exposure of adult males (C), and dermal exposure of adult females (D)

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