examination of serum markers for tissue and organ injuries indicated no significant changes compared to the vehicle group (Table S3). Administration of nZnO or $ZnCl_2$ to the lung led to a transient increase in serum Zn^{2+} concentration which returned to normal levels within 2 weeks after administration. The elevated serum Zn^{2+} did not affect the homeostasis of the other ions examined (Table S4).

Discussion

In vivo nanomaterial toxicity usually implicates oxidative stress, inflammation (Nel et al. 2006), and other biological responses depending on the individual nanomaterial. In vitro assays related to carcinogenicity, such as mammalian cell transformation and gene mutation assays, cannot represent the complex in vivo processes of different biological alterations and are not always suitable for risk assessment of nanomaterial carcinogenicity. In the present study, we tested the carcinogenic activity of nZnO in H*ras*128 rats by an initiation–promotion protocol, by which we previously found promotion effect of nanosized titanium dioxide on DHPN-induced lung and mammary carcinogenesis (Xu et al. 2010). nZnO did not show any promotion effects on lung proliferative or neoplastic lesions, indicating that nZnO is not carcinogenetic. Also, nZnO did not promote DHPN-induced mammary carcinogenesis.

On the other hand, nZnO was found to induce EHTB in H*ras*128 rats and wild-type SD rats. EHTB is a proliferative lesion of the terminal bronchiolar epithelium. It should be noted that the localization of EHTB was independent from that of DHPN-induced alveolar cell hyperplasia. This observation clearly indicates that the DHPN-induced alveolar cell hyperplasia and EHTB have different etiology, the latter being induced by nZnO. We also observed 2 cases of alveolar cell hyperplasia out of 6 cases in the nZnO alone group. This is not significant and thus considered to be spontaneous or an inflammation-associated event. The EHTB lesions regressed when administration of nZnO was discontinued and completely disappeared after 12 weeks. Along with EHTB, the interstitial inflammatory changes often observed surrounding the EHTB lesions also regressed. Our data and other reports (Cho et al. 2011) indicate that the EHTB lesions do not progress directly to cancers but are reactive proliferation associated with inflammatory events. Similar reversible inflammatory changes in the bronchoalveolar lavage fluids by administration of nanoscale or fine ZnO particles via inhalation or intratracheal instillation have previously been reported (Warheit et al. 2009).

nZnO particles were not found in alveolar macrophages, in the lung tissue, or in other organs, suggesting that the particles were dissolved to Zn^{2+}. Accordingly, we conducted experiments to determine whether Zn^{2+} would induce similar lesions. $ZnCl_2$ solution induced closely similar lung lesions and gene expression profiles as nZnO, demonstrating that the observed lung lesions were caused by Zn^{2+}. This was confirmed by increased Zn^{2+} level in the lung and serum after administration of nZnO. Interestingly, treatment with nZnO up-regulated the expression of the Omr1 gene in both the lung and the alveolar macrophages, and in vitro addition of Omr1-encoded AGP dose-dependently promoted nZnO dissolution. After Zn^{2+} was cleared from the lung, the EHTB and FAIP lesions disappeared, and this was evidenced by the positive correlation of EHTB number with Zn^{2+} content in the lung. Dissolution of nZnO has been reported to be particle size- and pH-dependent (Mudunkotuwa et al. 2012). Increased Omr1 expression possibly alters the microenvironment of the alveolar macrophages and the lung which accelerates nZnO dissolution. The elevated Zn^{2+} from nZnO dissolution possibly interferes with zinc ion homeostasis and leads to cytotoxic effects (Kao et al. 2012).

According to OSHA, the permissible exposure limit for zinc oxide particles is 15 mg/m^3 of air for total dust and 5 mg/m^3 for the respirable fraction (http://www.osha.gov/SLTC/healthguidelines/zincoxide/recognition.html). The inhalation exposure limit per kilogram of body weight per day for the respirable fraction is 192 μg, calculated from 6,000 ml of minute respiratory volume and 8 working hours for a 75 kg body weight worker. The dosing in the carcinogenesis study of the present study was approximately 35.5 and 71 μg/kg body weight a day (calculated from 125 to 250 μg every two weeks for a 250 g rat) and is lower than the OSHA limit for humans. Since nZnO has more potential to be ionized than larger ZnO particles because of its higher surface area (Mudunkotuwa et al. 2012), this feature should be taken into regulatory consideration.

It has been estimated that engineered nanomaterials will become a $1 trillion enterprise by 2015 (Nel et al. 2006), and ensuring health and environmental safety is a challenging task to the nanotechnology industry. Among numerous engineered nanomaterials, metal based or carbon based, most of which have been shown to have toxic effects to at least some extent, nZnO is a promising nanomaterial for biomedical applications. The results of the present study indicate that, although nZnO induced reversible lung toxicity, it did not cause carcinogenic or chronic progressive inflammatory lesions. Also, since it is biodegradable to ions, nZnO is easily cleared from the body (Rasmussen et al. 2010). Our study also suggests that the toxic effects of nZnO can be further decreased if efforts such as proper dosing and surface coating are made to lower the Zn^{2+} release from nZnO.

In conclusion, treatment of nZnO by IPS did not promote lung and mammary carcinogenesis in our carcinogenesis model. Although nZnO induced EHTB and FAIP, the lesions regressed rapidly along with clearance of surplus Zn^{2+} from the lung and serum. Thus, from a toxicological viewpoint, under the present experimental conditions, exposure of the lung to nZnO does not cause progressive neoplastic development or chronic fibrosis in the lung. These findings will be helpful in evaluating of the safety of nZnO used in biomedical applications, in which its use is of rather short duration, although long-term studies including inhalation studies are required to assess their occupational and environmental health hazards.

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Conflict of interest The authors declare that they have no conflict of interest.

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Carcinogenicity of perfluorooctanoic acid, tetrafluoroethylene, dichloromethane, 1,2-dichloropropane, and 1,3-propane sultone

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Declaration of interests
SMB has received research funding from the C8 class action settlement agreement between DuPont and plaintiffs; funds were administered by the Garden City Group that reports to the court (SMB's work was independent of either party in the lawsuit). SMB has also received funding from the National Institutes of Health, the California Air Resources Board, and the US Environmental Protection Agency.

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Declaration of interests
JWC has received research funding from the Association of Plastic Manufacturers Europe until 2012, European Chemical Industry Council, European

In June, 2014, 20 experts from nine countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to assess the carcinogenicity of perfluorooctanoic acid (PFOA), tetrafluoroethylene (TFE), dichloromethane (DCM), 1,2-dichloropropane (1,2-DCP), and 1,3-propane sultone (1,3-PS). These assessments will be published as volume 110 of the IARC Monographs.[1]

1,2-DCP is a synthetic chlorinated solvent, and a byproduct of the production of epichlorohydrin. It is used mainly as a chemical intermediate in the production of other organic chemicals such as propylene, carbon tetrachloride, and tetrachloroethylene, and in paint stripping, and was used as an ink-removal agent in the printing industry in Japan from the mid-1990s until 2012. 1,2-DCP was classified as carcinogenic to humans (Group 1), on the basis of sufficient evidence in humans that exposure to 1,2-DCP causes cholangiocarcinoma (biliary-tract cancer). The most important human evidence regarding carcinogenicity comes from studies of workers in a small offset printing plant in Osaka, Japan, where a very high risk of cholangiocarcinoma was reported.[2,3] Additional cases were later identified from several other printing plants. The major challenge in assessing the occurrence of cancer in the Japanese printing plants was to establish whether the observed excess of cholangiocarcinoma could be attributed to a specific agent. Although workers were exposed to more than 20 different chemicals, exposure to 1,2-DCP was common to all except one of the 24 patients with cholangiocarcinoma, and six of the patients had no known exposure to DCM (used together with 1,2-DCP in this industry). The working group considered the rarity of cholangiocarcinoma, the very high relative risk, the young ages of the patients, the absence of non-occupational risk factors, and the intensity of the exposure as indications that the excess of cholangiocarcinoma was unlikely to be the result of chance, bias, or non-occupational confounding. Sufficient evidence for carcinogenicity has also been reported in experimental animals, with malignant lung and hepatocellular tumours observed in exposed mice.[4,5] On the basis of this evidence, most of the working group concluded that 1,2-DCP was the causative agent responsible for the large excess of cholangiocarcinoma in the exposed workers. However, a minority concluded that the association between 1,2-DCP and cholangiocarcinoma was credible, but the role of other agents, mainly DCM, could not be separated with complete confidence. The working group members also noted that most of the evidence came from reports in just one plant.

DCM has been used in the manufacture of polycarbonate plastics, hydrofluorocarbons, synthetic fibres, and photographic films, as an aerosol propellant, for paint stripping, metal cleaning, and printing-ink removal, and as an extraction solvent for some foods. DCM was classified as probably carcinogenic to humans (Group 2A) on the basis of limited evidence that it causes biliary-tract cancer and non-Hodgkin lymphoma in humans and sufficient evidence of carcinogenicity in experimental animals (malignant lung and hepatocellular tumours in male and female mice).[2,3,6–9] In making its overall assessment, the working group also took into account the strong evidence that DCM metabolism via glutathione-S-transferase T1 (GSTT1) leads to the formation of reactive metabolites, that GSTT1 activity is strongly associated with genotoxicity of DCM in vitro and in vivo, and that GSTT1-mediated metabolism of DCM does occur in humans.

TFE is used mainly as an intermediate in the production of polytetrafluoroethylene, with application in a wide range of industrial and consumer products, including non-stick coatings and waterproof clothing. Despite the absence of adequate data on cancer in humans and weak mechanistic information, the working group's overall assessment of the carcinogenicity of TFE was upgraded from possibly carcinogenic to humans (Group 2B) to probably carcinogenic (Group 2A), on the basis of sufficient evidence in experimental animals with a striking and atypical pattern of tumours. Specifically, neoplasms at several sites and with very high incidence were noted in male and female rodents after exposure to TFE (mice: liver haemangiosarcoma, hepatocellular carcinoma, and histocytic sarcoma; rats: renal cell adenoma or carcinoma, hepatocellular carcinoma, mononuclear cell leukaemia, and the rare liver haemangiosarcoma [in female rats only]).[10]

1,3-PS has been used as an intermediate in the manufacture of other chemicals and a range of products including detergents, pesticides, pharmaceuticals, and photographic materials. Major industrial use has been largely terminated, but use in manufacturing lithium batteries has been reported recently. 1,3-PS was classified as probably carcinogenic to humans

(Group 2A), on the basis of inadequate evidence in humans and sufficient evidence in experimental animals with a mechanistic upgrade supported by strong evidence of genotoxicity. 1,3-PS causes malignant tumours of the skin and lymphohaematopoietic system in mice and malignant glioma in rats.[11,12] 1,3-PS is an alkylating agent that reacts directly with DNA and protein. DNA reactivity was evident in various genotoxicity assays, including in animals and in human cells in vitro. Because 1,3-PS does not require metabolic activation and reacts directly with DNA and other macromolecules, the working group concluded that this mechanism probably operates both in animals and humans.

PFOA and its salts are used in the production of fluoropolymers and in many industrial and commercial products, notably in producing non-stick cookware, waterproof clothing, and paper coatings used in food packaging. PFOA is persistent in the environment and has been detected worldwide at low concentrations in the general population. Additionally, communities near some production facilities have been highly exposed to PFOA as a result of emissions to air and water. On the basis of limited evidence in humans that PFOA causes testicular and renal cancer, and limited evidence in experimental animals, the working group classified PFOA as possibly carcinogenic to humans (Group 2B). Increased risk of kidney cancer with a statistically significant exposure–response trend was reported in workers in a fluoropolymer production plant in West Virginia, USA, and in an exposed community near the plant (relative risk 2·0, 95% CI 1·0–3·9).[13,14] Increases of about threefold in the risk of testicular cancer were reported in the most highly exposed residents of communities near the same plant.[14,15] The working group considered the evidence regarding mechanisms of PFOA-associated carcinogenesis to be moderate, which did not lead to a change in the overall classification of PFOA.

We declare no competing interests.

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International Agency for Research on Cancer, Lyon, France

1 International Agency for Research on Cancer. Volume 110: Perfluoro-octanoic acid, tetrafluoroethylene, dichloromethane, 1,2-dichloropropane, 1,3-propane sultone. IARC Working Group; Lyon, June 3–10, 2014. *IARC Monogr Eval Carcinog Risk Chem Hum* (in press).

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Carcinogenicity of fluoro-edenite, silicon carbide fibres and whiskers, and carbon nanotubes

In October, 2014, 21 experts from ten countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to assess the carcinogenicity of fluoro-edenite, silicon carbide (SiC) fibres and whiskers, and carbon nanotubes (CNTs) including single-walled (SWCNTs) and multi-walled (MWCNTs) types. These assessments will be published as Volume 111 of the IARC Monographs.[1]

Fluoro-edenite was first identified around the Etna volcano near Biancavilla, Italy; a similar mineral was also reported from the Kimpo volcano in Japan. Fluoro-edenite can occur as asbestiform fibres. Unpaved roads made from local quarry products from Biancavilla, used since the 1950s, are a source for airborne fluoro-edenite fibres; additionally indoor air was also contaminated from the use of the quarry's products in building materials. Several surveillance studies reported an excess of mesothelioma incidence and mortality in the regional population of Biancavilla.[2] Since the rate ratios for mesothelioma were large and stable, chance was unlikely to explain these findings. The excess was similar in men and women, and most prominent in young adults, suggesting an environmental rather than occupational cause. Moreover, most of the cases had no history of occupational exposure to asbestos. Fluoro-edenite fibrous amphibole was classified as carcinogenic to humans (Group 1) on the basis of sufficient evidence in humans that exposure to fluoro-edenite causes mesothelioma. Sufficient evidence of carcinogenicity was also reported in experimental animals, with increased incidences of mesotheliomas observed in one study in male and female rats given fibrous fluoro-edenite by intraperitoneal or intrapleural injection.[3] The results of the few available mechanistic studies were consistent with proposed mechanisms of fibre carcinogenicity.[4]

SiC occurs in several forms: particles, fibres, and whiskers. SiC particles are manufactured (mostly for use as industrial abrasive) mainly by the Acheson process, with SiC fibres being unwanted by-products. SiC fibres are generally poly-crystalline; of variable length and diameter, and may include fibres that are indistinguishable from whiskers. SiC whiskers are intentionally produced by different processes as durable industrial substitutes for asbestos; they are physically homogeneous and mono-crystalline, and their dimensions are similar to asbestos amphiboles. The carcinogenicity of SiC fibres was investigated in two cohorts of Acheson process workers who were exposed to fibrous and non-fibrous SiC, quartz, and cristobalite. In a Canadian cohort study,[5] an excess of lung cancer mortality was observed. An excess of lung cancer and an exposure–response relationship with SiC fibres was described in the most detailed report from a series of studies on cancer incidence in a Norwegian cohort.[6] The analyses were limited to workers with at least 3 years of employment in the plant and based on a detailed job-exposure matrix taking into account multiple exposures. The exposure–response relationship was somewhat weakened after adjustment for exposure to cristobalite. Occupational exposures associated with the Acheson process were classified as carcinogenic to humans (Group 1) on the basis of sufficient evidence in humans that they cause lung cancer. Since the correlation between exposures to SiC fibres and cristobalite made it difficult to disentangle their independent effects, the Working Group concluded that fibrous SiC is possibly carcinogenic to humans (Group 2B) based on limited evidence in humans that it causes lung cancer. No data on cancer in humans exposed to SiC whiskers were available. In experimental animals, there was sufficient evidence for the carcinogenicity of SiC whiskers, with mesotheliomas observed in three studies in female rats treated by intrapleural implantation,[7] intrapleural injection, or intraperitoneal injection, and in one inhalation study in rats that did not include concurrent controls. Although not unanimous, the Working Group classified SiC whiskers as probably carcinogenic to humans (Group 2A) rather than possibly carcinogenic to humans (Group 2B), on the basis that the physical properties of the whiskers resemble those of asbestos and erionite fibres, which are known carcinogens. In addition, the results of available mechanistic studies were consistent with proposed mechanisms of fibre carcinogenicity.[4] The majority of the Working Group considered that differences in the nature of SiC fibres and SiC whiskers warranted separate evaluations.

Carbon nanotubes may consist of either a single graphene cylinder (SWCNTs) with an outer diameter of 1–3 nm, or of multiple graphene cylinders arranged in concentric layers (MWCNTs) with diameters of 10–200 nm. CNTs are typically few micrometres in length, ranging from a few hundreds of nanometres to several tens of micrometres; their physical and chemical characteristics vary depending on the production technique. Applications include improving the structural properties of fabrics, plastics, rubbers, electronics, and composite materials. The highest release of CNTs, usually as entangled agglomerates which can be respirable, is observed during production and handling, and in cleaning of the production reactor. Measurement of occupational exposure is limited,

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March 3–10, 2015, Volume 112: Some organophosphate insecticides and herbicides: diazinon, glyphosate, malathion, parathion, and tetrachlorvinphos

June 2–9, 2015, Volume 113: Some organochlorine insecticides and some chlorphenoxy herbicides

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and consumer exposure was not quantified. No human cancer data were available to the Working Group, indicating inadequate evidence for the carcinogenicity of CNTs in humans. Some CNTs were tested in rodents. MWCNT-7 caused peritoneal mesotheliomas in male and female rats in one intraperitoneal injection study[8] and one intrascrotal injection study,[9] and in male *p53*$^{+/-}$ mice in two intraperitoneal injection studies.[10] Inhalation of MWCNT-7 promoted bronchioloalveolar adenoma and carcinoma in male mice.[11] In one intraperitoneal study, two other types of MWCNTs with physical dimensions similar to those of MWCNT-7 (length, 1–19 μm; diameter, 40–170 nm) caused mesotheliomas in male and female rats.[8] Two studies with SWCNTs in rats were inconclusive. Regarding carcinogenicity in experimental animals, the Working Group concluded that there was sufficient evidence for MWCNT-7, limited evidence for the two other types of MWCNTs with dimensions similar to MWCNT-7, and inadequate evidence for SWCNTs. Mechanistic and other data in rodents provided evidence of translocation of three types of MWCNTs (including MWCNT-7) to the pleura.[12] Additionally, inhalation of some MWCNTs or SWCNTs induced acute or persistent pulmonary inflammation, granuloma formation, fibrosis, and bronchiolar or bronchioloalveolar hyperplasia in rodents.[13,14] Studies in rodents (eg, Shvedova et al[15]) and in cultured human lung or mesothelial cells showed that MWCNTs, SWCNTs, or both induce genetic lesions such as DNA strand breaks, oxidised DNA bases, mutations, micronucleus formation, and chromosomal aberrations. SWCNTs and MWCNTs also perturb the cellular mitotic apparatus, including microtubules and centrosomes, in human lung epithelial cells.[16,17] As a whole, the Working Group acknowledged that the above mechanisms are all relevant to humans. However, a majority did not consider the mechanistic evidence for carcinogenicity—especially concerning chronic endpoints—to be strong for any specific CNT. Furthermore, the lack of coherent evidence across the various distinct CNTs precluded generalisation to other types of CNTs. Thus, MWCNT-7 was classified as possibly carcinogenic to humans (Group 2B); and SWCNTs and MWCNTs excluding MWCNT-7 were categorised as not classifiable as to their carcinogenicity to humans (Group 3).

We declare no competing interests.

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International Agency for Research on Cancer, Lyon, France

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