National Institute for Public Health
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Ministry of Health, Welfare and Sport

Knowledge brief

Occupational exposure to respirable dust

Assessment of the German MAK Commission report for the Health Council of the Netherlands

RIVM

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The Dutch Expert Commission on Occupational Standards (DECOS) of the Health Council of the Netherlands advises on health-based occupational exposure limits (OELs). Currently, an advice for an OEL for respirable dust for the workplace is being prepared. For this, the DECOS uses a report of the German MAK Commission[1] as a basis for its recommendations for an occupational exposure limit (OEL) for respirable dust (1).
The MAK Commission derived a MAK value of 0.3 mg/m^3 for the respirable dust fraction of biopersistent granular dusts with a density of 1 g/cm^3, using a two-part approach (1). The first part was based on a chronic inhalation toxicity study with toner dust and titanium dioxide (2). The second part, used as supportive evidence, was based on a publication by Pauluhn (2011) (3). However, the MAK approach was questioned in the scientific literature (4-6). The DECOS has asked RIVM for advice on the scientific approach used by the MAK Commission to derive the OEL for respirable dust, considering the scientific discussion that followed the publication of the MAK value. DECOS requested the use of the most recent version of lung particle deposition software model to recalculate the MAK value from the first part of the approach, including a documentation sufficient for independent reproduction of the used calculations to support the derivation of the OEL.

Specifically, the DECOS requested RIVM to address the following:

1) What is RIVM's assessment of both parts of the OEL derivation approach as performed by the MAK Commission?
2) What is RIVM's assessment of the underlying toxicity studies in the MAK Commission approach?
3) Which additional toxicity studies on biopersistent respirable dusts based on a selection made by the DECOS are also suitable for OEL derivation?
4) What would the Human Equivalent Concentration (HEC) be if a similar derivation was performed as done by the MAK Commission, but using the latest version of the Multiple-Path Particle Dosimetry (MPPD) model for the alveolar deposition fraction?
5) What are the HECs from the additional studies using part A of the MAK approach and the latest version of the MPPD model?
6) What is RIVM's assessment of factors that influence the derivation of the OEL in part A?

In addition to the DECOS questions, RIVM also discusses the comments from Morfeld *et al.* and response by Hartwig *et al.* (4-6). RIVM advises DECOS what parts of the OEL derivation could be adopted and calculates the HECs that serve as a starting point for the OEL derivation. RIVM does not perform the final OEL derivation.

[1] German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area

Background information on the MAK value for respirable dust

In 1997, the MAK Commission established a general threshold limit value for dust of 1.5 mg/m^3 for the respirable fraction. This limit value applies to poorly soluble or insoluble dusts that are not already covered by a substance specific OEL, and does not apply if toxic effects such as genotoxic, carcinogenic, fibrogenic, allergenic or other systemic-toxic effects of the dust are expected. This MAK limit value is intended to 'prevent the unspecific effects which all insoluble dusts can produce in the respiratory organs, effects such as impairment of airway clearance by overloading, chronic inflammatory changes in the bronchial mucosa and obstructive ventilation disorders'.
In 2011, the MAK value for respirable dust was re-evaluated, because new results from toxicity studies were available. The MAK value for respirable dust was reduced from 1.5 to 0.3 mg/m^3. This limit value applies to respirable biopersistent granular dust with a material density of 1 g/cm^3. This limit does not apply to ultrafine particles (particles with a constituent particle size smaller than 100 nanometer).

1. OEL derivation for respirable dust by the MAK Commission

Upon inhalation, biopersistent granular respirable dust particles deposit in the upper and lower airways. Particles deposited in the upper airways are cleared faster than those deposited in the lower airways, also referred to as the air exchange region or alveolar region. Prolonged presence (or particle retention) of biopersistent granular respirable particles in the alveoli is correlated with the occurrence of local inflammatory reactions, fibrosis and – at least in rodents – tumours after repeated inhalation.
The MAK Commission's reasoning when deriving a threshold limit value for biopersistent respirable particles was to prevent particle-induced inflammation and the resulting diverse proliferative tissue changes in the lungs from occurring in humans after chronic dust exposure. The MAK Commission applied a two-part approach for the derivation of such a threshold limit value:

A. The first part was based on animal exposures to biopersistent respirable particles that does not lead to adverse health effects. As the adverse health effect of the dust, the inflammatory proliferative response in the rat lung was chosen by the MAK Commission; the No Observed Adverse Effect Concentration (NOAEC) should not induce a significant increase in inflammatory cells, inflammation-specific cytokines, enzymes specific to cytotoxicity or hyperplasia of the pulmonary epithelium. A chronic inhalation study with toner and TiO_2 in the rat was selected as the key study (2). NOAECs were extrapolated to a human-equivalent exposure concentration (HEC) by applying adjustment factors for species differences that influence the internal lung dose. These factors include differences in breathing parameters, lung surface area, pulmonary clearance rates, and pulmonary deposition fraction, which was estimated using MPPD lung particle deposition software.

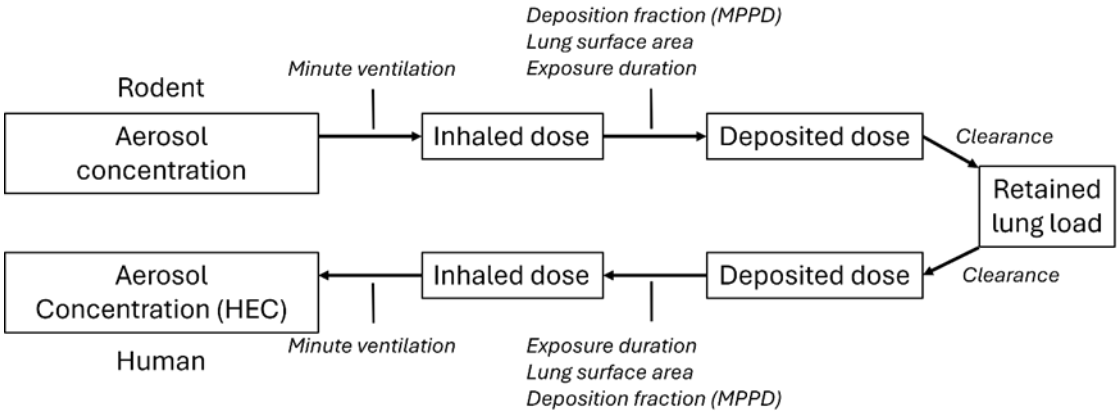
Multiple-Path Particle Dosimetry (MPPD) model
The MPPD model is publicly available as an application that has been developed by the CIIT Centers for Health Research (CIIT), USA, in collaboration with the National Institute of Public Health and the Environment (RIVM), the Netherlands. It is used to predict the deposition of particles between 0.001 and 100 µm in diameter in the human and rat respiratory tract. The computer models are constructed using information on the size and shape of human and rat lung (so-called morphometric data).

The model considers particle deposition in the lung by mechanisms of impaction, sedimentation and diffusion. Model input parameters include species specific airways morphology, particle properties (size distribution, density, aerosol concentration) and

species-specific breathing conditions (tidal volume, breathing frequency, and mode of breathing – e.g. nasal/oral/oronasal).

By assuming similar sensitivity in rats and humans for the particle-induced effects in the lungs, the MAK Commission calculated a corresponding human equivalent particle dose per m^2 lung surface area that does not lead to adverse effects. From this particle dose, an aerosol concentration of respirable particles was calculated that, over a human working lifetime, would not lead to adverse health effects (Figure 1). The derived OELs were 0.11 mg/m^3 for toner and 0.25 mg/m^3 for TiO_2 (adjusted to a density of 1 g/cm^3).

Figure 1 Schematic summary of part A based on the calculation of a lung load in the rat that prevents lung inflammation, assuming similar sensitivity in the human lung, by dividing the species specific lung particle deposited dose by the species clearance rate and back calculate that to Human Equivalent aerosol Concentration (HEC) for workers. Minute ventilation is tidal volume times the breathing frequency. In the MAK Commission approach the HEC is also the OEL.



B. The second part was based on assessment of the retained particle volume per macrophage pool volume in the lung. For this, a generic model was developed that could predict the air concentration where the retained dust particle volume would not exceed the filling of the alveolar macrophage volume by 6% (3). The underlying hypothesis is that below this level, there are no adverse effects in the lung after exposure to biopersistent granular dusts. The resulting OEL following this calculation was 0.5 mg/m^3.

The MAK Commission averaged the OELs from part A and B, resulting in a rounded occupational threshold limit value of 0.3 mg/m^3 for the respirable dust fraction of biopersistent granular dusts with a material density of 1 g/cm^3.

1.1 RIVM assessment of the OEL derivation in part A

The particle dose per m^2 lung surface area was calculated for rats at the NOAEC, and the human equivalent concentration (HEC) was then derived by accounting for species-specific differences in pulmonary deposition (using MPPD modeling), breathing parameters, lung surface area, and pulmonary clearance (see Figure 1). The MAK Commission assumed rats and humans have similar sensitivity when exposure is expressed as particle dose per m^2 lung surface area. The particle lung load in the alveolar region is determined by the particle deposition rate (assumed constant rate derived from the deposited fraction and duration of exposure) divided by the species-specific alveolar clearance rate. While respirable particles also deposit in the upper airways, the critical effect of lung inflammation is observed in the lower respiratory tract, specifically the alveoli. RIVM finds the different steps in the

calculation as presented in the MAK Commission document ambiguous to follow. The MAK Commission refers to a (steady state) lung load expressed by volume (m^3), while a unit of mass is expected. However, by using the same assumptions as the MAK Commission, RIVM arrives at the same HECs based on the following calculations:

- The rat inhales a total volume of 0.055 m^3 per day (minute ventilation {tidal volume [2.1 ml] x breathing frequency [102 breaths/min] x exposure duration [360 min/day] x 5/7 [exposure days/week] x 10E-6)
- For **toner**, a concentration of 1 mg/m^3 (NOAEC rat based on Muhle *et al*. 1991)(2), a pulmonary deposition of 3.88% (modelled by MAK using MPPD v2.0), and a lung surface area 0.297 m^2 for the rat, leads to a dose per m^2 lung surface area of 1 x 0.055 x 0.0388 / 0.297 = 0.0072 mg/m^2.
- Using this dose per m^2, extrapolation to humans using a human lung surface area of 57.22 m^2, a pulmonary deposition of 7.01% (modelled by MAK for using MPPD v2.0), and an inhaled volume of 6.58 m^3 per day (10 m^3/8 hour working day x 240/365 working days/year), leads to a HEC of 0.0072 x 57.22 / (0.0701 x 6.58) = 0.89 mg/m^3.
- If then a 6.7-fold higher clearance rate in rats vs humans is taken into account (which is based on elimination half-times of 60 days in rats and 400 days in humans, with clearance = -ln(0.5)/$t_{1/2}$), this translates to a HEC of 0.89 / 6.7 = 0.133 mg/m^3 for toner (density 1.2 g/cm^3).
- For **TiO_2** (density 4.3 g/cm^3), using a NOAEC of 5 mg/m^3, a pulmonary deposition of 8.72% for rats and 9.92% for humans (modelled by MAK for using MPPD v2.0) in the calculation above with species specific numbers for lung surface area and clearance results in a HEC of 1.066 mg/m^3.
- These values were subsequently divided by the density, resulting in HECs and OELs of 0.11 mg/m^3 (toner) and 0.25 mg/m^3 (TiO_2) for a material density of 1 g/cm^3. The MAK Commission does not apply an assessment factor for intraspecies differences; therefore, the HEC in that case is the OEL. Assessment factors for study duration or LOAEC to NOAEC correction were not needed, as the studies used chronic 2-year exposure and NOAECs were identified.

Additional reflections on choices for species-specific factors and the application of a correction for density are given under point 4.

1.2 RIVM assessment of part B and its critique by Morfeld et al 2015 and 2016

The MAK Commission's part B is based on the derivation of a generic particle NOAEC for the rat ($NOAEC_A$). It is proposed by Pauluhn 2011 to be obtained by deriving an air concentration that leads to a retained particle volume that stays below 6% of the internal volume of an alveolar macrophage (3). This particle volume corresponds to 1 microliter of particles per gram lung. The particle volume is not determined by the material or bulk density, but by the "space taken up by particles" or the volume of displacement within the macrophage. This is known as the specific agglomerate density of particles.
The retained particle volume follows from how many particles of the total end up in the alveolar region (the alveolar deposition fraction) multiplied by the volume of air per breath (tidal volume) and the number of breaths per day (respiratory rate) minus the estimated clearance.

The above description of the calculation is rearranged and presented in the MAK documentation (3) in the following formula:

$$NO(A)EC_A = \frac{1\ \mu l}{0,29\ m^3} \times \frac{\rho}{f_{vi}} \times \frac{100}{PM_{resp}} \left[\frac{mg}{m^3}\right]$$

RIVM cannot reproduce the rearrangement of the formula. For example, alveolar clearance is needed to estimate the retained particle volume, but the formula does not explicitly mention this term, so it cannot be appreciated by looking at the formula which input for alveolar clearance was chosen.
The 1 µl term in the formula represents the alveolar macrophage volumetric limit at 6% of the distribution volume (= the pool of alveolar macrophages (AM) that has accumulated an average volume of particles over 6% of their total cellular volume). It is unclear what the unit of this term is: per gram lung or per kilogram rat. RIVM agrees with Morfeld 2015, that there is a mistake in this part of the formula. According to Oberdörster *et al.,* 1 µl/gram lung corresponds to 6% of the alveolar macrophage volume (7). If µl/kg rat was meant, this part of the formula would become unitless as it cancels the unit below, but the value should then be corrected by a factor of 4.2. According to Morrow: the original overload volume threshold was set to 6% of the alveolar macrophage pool volume: 6% × 70 µl/kg rat = 4.2 µl/kg rat. Subsequently, the $NOAEC_A$ should be multiplied by the same factor of 4.2.
Then f_{vi} is the fraction of the particle volume that has to be inhaled per exposure day to attain the cumulative overload threshold at the end of the exposure period (3). The cumulative factor 'f' depends on the study period and is 17.5, 40 and 61 for rat inhalation studies with 6 hours/day, 5 times/week for 4, 13, and 104 weeks, respectively. Pauluhn 2011 does not provide an explanation of how this fraction is derived. It is likely that this factor is derived using a clearance estimation. This clearance is estimated by using a piece of software code that is not presented in the MAK Commission report nor in the original publication and can't be traced or verified.
Also, $100/PM_{resp}$ accounts for the total particle concentration potentially respirable in inhalation chambers and is expressed as the inverted alveolar deposition fraction estimated by MPPD-V2.0 lung deposition model. The exact parameters in MPPD-V2.0 that have been selected to estimate the alveolar deposition fraction in the lung are not given in the MAK Commission report nor in Pauluhn 2011, which makes it impossible to verify the output. Morfeld *et al.* 2015 has attempted to recreate the results by choosing different settings of the MPPD model and concluded that the settings probably were "Oronasal-Mouth Breather" to characterize the breathing pattern in humans, instead of "Oronasal-Normal Augmenter" with the "inhalability adjustment" switched off in the program. Switching the inhalability adjustment 'on' is recommended by the MAK Commission report in part A and by the MPPD lung deposition model. RIVM also advises modelling lung deposition with the inhalability adjustment switched on.

1.3 General comments on the MAK Commission approach
The MAK Commission derived the OEL based on animal models and has chosen the endpoint of lung inflammation as the basis (4). The MAK Commission chose particle volume as the relevant dose metric for risk assessment. Morfeld *et al.* 2015 indicated that: "particle surface area was not investigated, despite toxicological evidence in favour of this metric". RIVM considers the choice for a generic model based on particle volume valid for larger-sized particles as it correlates to reduced removal of particles by alveolar macrophages from the lung (impaired clearance), as was postulated by Morrow *et al.* (8). For smaller-sized particles (i.e. nanoparticles, having a constituent particle size smaller than 100 nanometer), good correlations with other metrics such as particle surface area have been found (9, 10) and there is ongoing debate on the best dose metric to describe particle effects after inhalation (11).
The MAK Commission chose particle-induced inflammation and the resulting diverse proliferative tissue changes as the relevant health endpoint. Morfeld *et al.* 2015 stated that: "The prominent role given to the BALF polymorphonuclear neutrophils (PMNs) in relation to the particle lung exposure in rats does not correspond to BAL results in

humans". There are known species differences between rat and human particle handling by the lung and particle retainment in different lung compartments, as well as uncertainties related to whether some events take place in humans or not. The rat BALF PMN may not translate one on one to a human response, but lung inflammation caused by particles in humans has been observed in workers exposed to coal dust and crystalline silica (summarized in (12)). In addition, BAL (bronchoalveolar lavage) analysis is used as clinical tool to assess lung disease in humans. There are indications that a neutrophil increase in BAL is biological relevant, since a 4% PMN increase has been associated with respiratory impairment in workers in dusty jobs (13). In workers, a 10-year cumulative exposure to nanomaterials is associated with worse pulmonary function with indications of mediation of the effect via pulmonary inflammation (14). Rats respond to biopersistent dust with more chronic inflammation and epithelial type II cell proliferation and relatively less fibrosis when compared to humans. However, here the dose threshold preventing the initial inflammation in the rat lung is considered to also prevent the initial inflammation in the human lung as well as subsequent effects such as fibrosis (12).

2. Rat inhalation studies as basis for OEL derivation in part A

2.1 Chronic inhalation of toner and TiO_2

The underlying study selected by the MAK Commission for part A is a chronic (2-year) inhalation toxicity study conducted according to OECD Guidelines (2). Two materials were tested: 1) a toner (Xerox 9000) consisting of 90% polymer particles (CAS 25213-39-2) and 10% furnace-type carbon black, and 2) a pigment grade TiO_2 (Bayertitan T). Particle characteristics and study details are summarized in Table 1.

The constituent particle sizes of the materials were not provided in the studies. For toner, the constituent particle size was likely in the micrometer range, given the MMAD of 4.0 µm and the fact that toners used to be produced in micrometer size and fractionation was applied to reduce the particle size. For TiO_2, its size was likely above 100 nanometer (and therefore relevant to use for the derivation) as the material was referred to as pigment grade. The aerodynamic particle size distributions of the respective aerosols – i.e. mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) – were provided for both materials and were within the respirable range.

Table 1 Particle characteristics and study details in key study Muhle et al. 1991 for part A

Material	**Study details**	**Suitability**
Toner Xerox 9000 (polymer plus carbon black)	- *Exposure*: 6 h/day, 5 d/wk, 24 months (whole-body) - *Actual air concentrations (mean* ± SD*)*: 0, 1.0 ± 0.1, 4.1 ± 0.1 and 16.0 ± 0.9 mg/m^3 - *Effect assessment*: end of exposure and month 26, plus intermediate sacrifices at 3, 6, 9, 12, 15 ,18 and 21 months. - *Particle size*: MMAD (GSD): 4.0 µm (1.5) - *Material density:* 1.2 g/cm^3	Constituent particle size is unknown; agglomerate particle size is respirable. NOAEC 1 mg/m^3
TiO_2 Bayertitan T (rutile)	- *Exposure*: 6 h/day, 5 d/wk, 24 months (whole-body) - *Actual air concentrations*: 0 and 5.0 ± 0.7 mg/m^3 - *Effect assessment*: end of exposure and month 26, plus intermediate sacrifices at 3, 6, 9, 12, 15 ,18 and 21 months. - *Particle size*: MMAD (GSD): 1.1 µm (1.6) - *Material density:* 4.3 g/cm^3	NOAEC 5 mg/m^3 (based on single concentration tested, true NOAEC could be higher)

A NOAEC of 1 mg/m^3 (toner dust) was derived based on the absence of lung fibrosis and no increase in the percentage of neutrophils and lymphocytes during the exposure period, directly after the 2-year exposure of Fisher F344 rats and 6 weeks after the end

of exposure. The LOAEC, based on these endpoints assessed directly after the 2-yr exposure, was 4.1 mg/m^3. In addition, significantly increased levels of minimal (incidence of 12.5 % animals) and mild (9.1%) fibrosis was seen at the LOAEC compared to controls. Cytotoxicity was detected only at the highest exposure concentration of 16 mg/m^3 based on increase in protein, LDH and β-glucoronidase in bronchoalveolar lavage fluid (BALF).
A NOAEC of 5 mg/m^3 (pigment grade TiO_2) was derived by the MAK Commission based on the absence of lung fibrosis, absence of cytotoxicity and a transient increase in the % neutrophils after 15 months of exposure of Fisher F344 rats that was no longer detected after longer exposure or after the end of the exposure period. The presentation of the results in tabular format did not allow for more in-depth evaluation of this transient effect. As the effects for the biopersistent granular dusts presented here have been evaluated at the end of the exposure period, the absence of effect for TiO_2 was likewise determined at the same timepoint and therefore served as the NOAEC.

2.2 Assessment of additional studies on respirable dust
Additional studies on biopersistent granular dust were selected by the DECOS (Table 2). An assessment of the studies was made by RIVM with the following aspects in mind:
- The constituent particle size of the test material should be above 100 nanometer, and the aerodynamic particle size distribution should be in the respirable range.
- The study is conducted in rats, since the rat is the most sensitive species for particulate effects (15), is the preferred species in the current OECD inhalation Test Guidelines.
- Study duration: Chronic exposure (2 yrs) is preferred over subchronic (90 day) exposure. Subacute (28-day) studies were not included, because the application of several assessment factors reduces the reliability of the outcome. A study design that includes a recovery period is informative to estimate the severity of observed effects, whether inflammatory effects are persistent or recover after the exposure is stopped.
- As the adverse health effect of the dust, the inflammatory proliferative response in the rat lung was selected by the MAK Commission; the NOAEC should not induce a significant increase in inflammatory cells, inflammation-specific cytokines, enzymes specific to cytotoxicity or hyperplasia of the pulmonary epithelium. It is not specified by the MAK Commission in the text whether this lack of effect should be observed directly after the end of exposure or after a recovery period. RIVM has chosen to evaluate all studies consistently on inflammation detected at the (earliest) timepoint after stopping exposure. Neutrophilic inflammation is still considered adverse even if it is resolved after a recovery period, since workers may not have such a recovery period during exposure over their entire working life.
- If no NOAEC could be identified, a Lowest Observed Adverse Effect (LOAEC) should be identified with subsequent application of an additional assessment factor (AF).
Per study, RIVM's considerations on its suitability to support OEL derivation are given (Table 2).

Table 2 Summary of additional inhalation studies to support part A derivation of the OEL

Material	**Study details**	**Suitability**
Pigment grade TiO_2 (Bermudez 2002)	*Exposure*: 6 h/day, 5 d/wk, 90 days (whole-body) *Target air conc*: 0, 10, 50 or 250 mg/m^3 *Actual air conc* (mean ± SD): 9.6 ± 1.1, 47.7 ± 5.1, 240.3 ± 20.0 mg/m^3 *Effect assessment*: directly after exposure and after 1 year *Constituent particle size*: ~300 nm. *Particle aerosol size*: MMAD (GSD) 1.44 µm (1.71)	+ Particle size range + Study in rats - sub-chronic study - 9.6 mg/m^3 is the LOAEC. Note: Particle density not reported; 4.3 g/cm^3

Material	Study details	Suitability
	Material density: 4.3 g/cm^3	was used for MPPD modelling.
Fe_3O_4 magnetite, Ferroxide® black 88P (Pauluhn 2012)	*Exposure*: 6 h/day, 5 d/wk, 90 days (nose-only) *Target air conc*: 0, 5, 15 and 50 mg/m^3 *Actual air conc* (mean ± SD): 4.7 ± 0.6, 16.6 ± 3.0 and 52.1 ± 6.4 mg/m^3 *Effect assessment*: at the end of 13 to 14-week exposure *Constituent particle size*: 300-600 nm. *Particle aerosol size*: MMAD (GSD) 1.30 µm (2.0) *Agglomerate density*: 4.6 g/cm^3	+ Particle size range + Study in rats - sub-chronic study - 4.7 mg/m^3 is the LOAEC.
CeO_2 (US EPA report, NRL data)	*Exposure*: 6 h/day, 5 d/wk, 90 days (nose-only) *Target air conc:* 0, 5 and 50 mg/m^3 *Actual air conc* (mean):0, 5.0, 50.5 and 507.5 mg/m^3 *Effect assessment*: after exposure? *Constituent particle size*: not reported. *Particle aerosol size* MMAD (GSD) 2.0 µm (1.85) *Material density*: 7.65 g/cm^3	+ Particle size range + Study in rats - sub-chronic study NOAEC is 5 mg/m^3 based on histopathology. BAL was not analysed.

TiO_2 (Bermudez 2002) (15): The agglomerate density was not reported, but RIVM assumes the same value for the material density of 4.3 g/cm^3 as for TiO_2 Bayertitan (2). The percentage of neutrophils in BALF was slightly, but statistically significantly elevated (exact number is difficult to read from the graph but it is likely less than 5% compared to controls (0.3%)) directly after the end of exposure (0 weeks) at 9.6 mg/m^3 and higher, but returned to baseline levels from post-exposure week 4 and onwards. At 47.7 and 239.1 mg/m^3, the percentage of neutrophils remained elevated during the entire duration of the recovery period together with a variety of lung lesions. No changes in other BAL parameters (cytology, LDH, total protein) or any histopathological changes in the lungs were observed at 9.6 mg/m^3. Therefore, the authors placed the NOAEC at 9.6 mg/m^3. If the small but statistically significant increase in neutrophils at the end of the exposure is considered adverse – which is advised by RIVM – 9.6 mg/m^3 should be considered as the LOAEC.

Fe_3O_4 (Pauluhn 2012) (16): The iron oxide pigment utilized in this study was from a technical production that utilized precipitation and drying and is potentially more soluble than those produced by calcination. The pigment properties (color and hue) are met best for particle sizes in the range of 0.1–1 µm. Different densities were provided in Pauluhn 2012. An agglomerate density of 4.6 g/cm^3, determined by Hg-pyknometry, was used in MPPD modelling. Details of a prior 28-day study using the same material were not included, because of the relatively short duration. In the 13-week study, elevations of neutrophils in BAL appeared to be the most sensitive endpoint. Statistically significant differences compared to controls were found at the lowest concentration tested (Table 6 in (16)); BAL PMN percentages were 3.2% and 3.7% in males and females exposed at 4.7 mg/m^3, respectively. It is not clear how much time there was between ending the exposure and the measurement of the BAL PMNs. Histopathological findings at this concentration included increased broncho-alveolar hypercellularity, black alveolar macrophages and black pigmentation of the lung-associated lymph nodes. The author derived an empirical NOAEL of 4.7 mg/m^3. Given the BAL and histopathology findings at the low concentration, RIVM considers 4.7 mg/m^3 to be the LOAEC.

CeO_2 (US EPA) (17): The constituent particle size was not reported. Alveolar hyperplasia was detected in 1 out of 15 males at the lowest concentration, but not in females. At 50.5 mg/m^3, this hyperplasia was observed in 11 out of 15 males and 5 out of 15 females together with an increase in relative and absolute lung weights. Based on the lung pathology, the NOAEC was 5 mg/m^3. Note that the most sensitive measurement in other studies – BAL neutrophils – was not included in this study.

3. Application of updated deposition fraction model in part A

The latest version MPPD 3.04 has been applied here to model the pulmonary deposition fraction for rats (i.e. the fraction of the aerosol mass that is deposited in the lungs) and humans. The deposition fraction is independent of the air concentration. Input parameters that were varied, based on study specific data, were particle size distribution (MMAD, GSD) and particle density; for most other parameters, species-specific default settings of the MPPD model were used (in line with MAK, 2014). The model was run for toner and TiO_2 (2) using the same input parameters as used by the MAK Commission (DFG, 2014). For the rat, the "Asymm. Multiple-Path Long-Evans" airway morphometry model was chosen, as this was considered closest to the "Asymm. Multiple Path" model (also based on the Long-Evans rat) used by the MAK Commission in the older version of the MPPD model. For toner, this resulted in deposition fractions in the lungs (P-fraction) of 0.0064 for the rat and 0.0744 for humans. For TiO_2, deposition fractions of 0.0711 for the rat and 0.1046 for humans were obtained (settings and results of the MPPD v3.04 modelling are given in Supplementary Table 1 in the Appendix). Based on these deposition fractions and the equations used in MAK part A (see Chapter 1.1.), HECs of 0.021 mg/m^3 for toner (density 1.2 g/cm^3) and 0.823 mg/m^3 for TiO_2 (density 4.3 g/cm^3) were derived, or when corrected for a density of 1, values of 0.017 mg/m^3 for toner and 0.19 mg/m^3 for TiO_2.

The recalculated limit value for TiO_2 is relatively close to the MAK value of 0.25 mg/m^3, whereas the recalculated limit value for toner is ~6.5 fold lower than the value derived by the MAK Commission, due to a lower pulmonary deposition modelled with MPPD v3.04. The developers of the MPPD model at Applied Research Associates, Inc. (Owen Price, AMA Division, Applied Research Associates, Inc., Arlington, VA) were contacted to verify these findings. They confirmed our findings and explained the ~6.5-fold difference due to the combination of two reasons: 1) a relatively large particle size (4.0 µm MMAD for toner) leading to a relatively low deposited dose, and 2) a fix to the rat upper respiratory tract deposition efficiency (impaction) curve in the latest MPPD model. Basically, the older version used by the MAK Commission (MPPD v2.0) underestimated the deposition in the upper respiratory tract for larger particles in the rat (and thus overestimated the deposition in the pulmonary region).

4. Influence of species-specific factors and post-hoc density correction on OEL derivation

Several species-specific factors in the calculation that influence the outcome of part A have been evaluated (Table 3). In addition, RIVM has evaluated the post-hoc density correction proposed by the MAK Commission.

Table 3 Overview of species-specific factors in HEC calculation

Factor	**Source**	**Rat**	**Human**
Deposition fraction	MPPD modelling (Version 2.0 used by MAK,	Rat airway morphometry model (based on Long-Evans rat)	Human airway morphometry model (based on lung cast 60 yr old male of 80 kg)

Factor	Source	Rat	Human
	version 3.04 by RIVM)		
minute ventilation x exposure duration = daily respiratory volume	Standard from MAK document	0.055 m^3 (360 min/day, 5 days/week)	6.58 m^3 (light exercise, 8 hours/ day, 5 days /week, 240 days/year)
Alveolar surface area	MAK document Mohrfeld 2015	0.297 m^2 -> suggested adaptation to **0.41 m^2**	57.22 m^2 -> suggested adaptation to **143 m^2**
Alveolar elimination half-time	MAK document Mohrfeld 2015	60 days	400 days -> suggested adaptation to **255 days**

RIVM has updated the calculation of the modelled deposition fraction using the latest version of the MPPD software and has used the same standard values for daily respiratory volume as presented in the MAK document. Different values for alveolar surface area and alveolar elimination half-time compared to the MAK document were chosen as discussed below.

4.1 Alveolar surface area
The MAK Commission used an alveolar surface area of 57.22 m^2 for humans and 0.297 m^2 for rats (18), which leads to a surface area ratio (i.e. translation factor) of 57.22/0.297 = 193. The value for rats was based on the alveolar surface area of one Long-Evans rat. Morfeld *et al.* (4, 6) stated that *the lung surface area values are not evidence based* and referred to a study by Stone *et al.* (1992) who investigated 4 Fischer rats (the strain also used by Muhle *et al.*, 1991) and 8 Sprague-Dawley rats, and determined the alveolar surface area using an *in situ* instillation method, in line with standard procedures endorsed by the American Thoracic Society and the European Respiratory Society (19). This resulted in a alveolar lung surface area of 0.41 (± 0.04) m^2 (Fischer rat) and 0.4 (± 0.03) m^2 (SD rat). The same method was used by Gehr *et al.* (1978) to determine human alveolar surface area, resulting in 143 (± 12) m^2, based on the analysis of the lungs of 8 humans (20). Based on these values, Morfeld *et al.* calculated a translation factor of 143/0.41=349, and argued that this was more suitable for OEL derivation, because it was determined by internationally recognized methods, in the same way for humans and rats, and applicable for the strain used in the toxicological study by Muhle *et al.*
RIVM advises selecting a value for rat alveolar surface area that is based on measurements on more than a single rat. In addition, using a similar technique to prepare the lung tissue in rats and humans (*in situ* instillation method) is advisable. This results in a translation factor of 349 as proposed by Morfeld *et al.* (4) and a higher HEC.

4.2. Alveolar elimination half-time
Particle-loaded alveolar macrophages are eliminated by rats with an elimination half-time of about 60 days (21). For humans, the MAK Commission chose an elimination half-time of 400 days. Although higher numbers of ≥700 days have been reported in literature, these values were likely increased due to macrophage toxicity. Morfeld *et al.* argued that the applied value for human alveolar clearance half time of 400 days is too large and referred to Gregoratto *et al.* (2010) for a more reliable estimate of 255 days for overall alveolar clearance, which – in addition to alveolar to bronchial clearance – also takes clearance to the interstitium into account (22). In addition, a value of approximately 250 days is supported by a general allometric scaling procedure proposed by West *et al.* (2002) (23). RIVM notes that, although this faster elimination half-time incorporates the translocation of particles from the alveolus to the interstitium, this does not equal elimination from the

body. Particles in the interstitium, could still exert biological effects. On the other hand, the critical effect chosen for the derivation of the OEL occurs in the alveolar compartment. Since there are good arguments for both values, RIVM will use both numbers for the derivation of the HEC.

4.3 Post-hoc density adjustment of the derived HEC values.
The MAK Commission used a one-compartment model in which the steady state lung load is dependent on 1) the mean deposition rate and 2) the alveolar clearance rate. Morfeld *et al.* showed that the deposition fraction – which determines the deposition rate – is largely independent of the density: pulmonary deposition, modelled using MPPD version 2.0 for a range of densities using data for toner as input, increased only marginally from 4.0 to 4.2% with density increasing from 1 to 5 g/cm^3. Morfeld *et al.* further point out that the MAK Commission applied identical clearance rates ($t_{1/2}$ of 60 days for toner and TiO_2 in rats despite the different densities; 400 days in humans), implying that particle clearance – and thus also the HEC – is also independent of the density.
RIVM agrees that assuming identical clearance rates for particles with different densities implies that particle clearance is independent of the density. In addition, the aerodynamic particle size of particles in air (MMAD) is dependent on the actual density of the particle agglomerates. Therefore, when determining the MMAD (GSD) at the workplace and relate this to the MMAD in the animal studies, this already includes (agglomerate) density.
To provide insight into the dependency of pulmonary deposition and HEC on particle density, RIVM modelled the pulmonary deposition for various hypothetical densities of toner and TiO_2 - while keeping all other input data constant - using the latest version of the MPPD model (v3.04), and subsequently calculated the HEC based on MAK part A with and without applying a correction for density (Table 4). Variations in particle density were found to have a very limited effect on the alveolar deposition fraction. Even at extreme hypothetical densities, changes in density had very little influence on the deposition fraction for particles with a larger MMAD such as toner and only became slightly more pronounced for particles with a lower MMAD, such as TiO_2. Consequently, this resulted in only minor differences on the HECs calculated without density correction. However, when a post-hoc density correction was applied, the range of calculated HECs increased substantially across varying densities. Based on these findings, RIVM recommends not to apply a post-hoc density adjustment to the derived HECs.

Table 4: Pulmonary deposition fractions and HECs for different hypothetical particles densities

	Toner (MMAD 4.0 µm; GSD 1.5)				TiO_2 (MMAD 1.1 µm; GSD 1.6)			
	P-fraction		HEC_{MAK} (mg/m^3)		P-fraction		HEC_{MAK} (mg/m^3)	
Density (g/cm^3)	rat	human	w/o ρ-corr.	ρ-corr.	rat	human	w/o ρ-corr.	ρ-corr.
0.1	0.0059	0.0725	0.020	0.197	0.0390	0.0698	0.676	6.763
1	0.0064	0.0742	0.021	0.021	0.0532	0.0850	0.758	0.758
5	0.0070	0.0768	0.022	0.004	0.0736	0.1074	0.829	0.166
20	0.0080	0.0807	0.024	0.001	0.1039	0.1440	0.873	0.044

P-fraction: the fraction of the aerosol mass that is deposited in the lungs.
HEC_{MAK}: HEC calculated based on MAK part A, except for pulmonary deposition which was modelled using the MPPD v3.04; ρ-corr: with (or w/o: without) post-hoc correction for density.

4.4 Influence of updated deposited fraction, species-specific factors and post-hoc density correction on HEC values
A summary of the NOAECs and LOAECs from the studies and the subsequent HECs that can serve as input for OEL setting is given in table 5 and 6. Here, the HECs for toner and

TiO_2 are recalculated using the latest version of the MPPD model following part A of the MAK Commission approach (without applying assessment factors). This is supplemented with data from the newly added studies on TiO_2, Fe_3O_4 and CeO_2. To illustrate how some of the input choices affect the outcome, HECs were calculated for various (combinations of) values for lung surface area (rat and human) and human alveolar clearance rate, both with (Table 6) and without (Table 5) applying a post-hoc correction for density. Note that interspecies differences such as difference in lung surface area, lung clearance rate and lung deposition are accounted for in part A calculations. Intraspecies differences such as toxicodynamic differences are not accounted for as RIVM, like the MAK Commission, assumes that the response in rats and humans is the same. All inhalation exposures in the rat were 6 hours per day, therefore no correction is needed to equalize HEC values between different rat studies.

Table 5 Summary of NOAEC/LOAECs from studies, with HECs calculated for different options of lung surface area and human alveolar clearance rate, ***without*** *post-hoc density correction, for possible use by DECOS as a basis for OEL derivation. Note: assessment factors for extrapolation of LOAEC to NOAEC, and subchronic to chronic exposure are not yet applied (and hence it is difficult to directly compare HECs derived from different studies).*

Lung surface, rat and human:			**0.297 and 57.22 m^2**		**0.41 and 143 m^2**	
Alveolar clearance, humans ($t_{1/2}$):			**400 d**	**255 d**	**400 d**	**255 d**
Material	**Duration**	**NOAEC/ LOAEC**	**HEC (mg/m^3)**	**HEC (mg/m^3)**	**HEC (mg/m^3)**	**HEC (mg/m^3)**
Toner [Muhle]	Chronic	NOAEC = 1 mg/m^3	0.021	0.033	0.038	0.059
TiO_2 [Muhle]	Chronic	NOAEC = 5 mg/m^3	0.823	1.291	1.489	2.336
CeO_2 [EPA]	Subchronic #	NOAEC = 5 mg/m^3	0.500	0.784	0.905	1.420
TiO_2 [Bermudez]	Subchronic #	LOAEC = 9.6 mg/m^3 *	1.214	1.905	2.198	3.449
Fe_3O_4 [Pauluhn]	Subchronic #	LOAEC = 4.7 mg/m^3 *	0.643	1.009	1.165	1.827

assessment factor needed to correct for duration from subchronic to chronic.
* assessment factor needed to correct for LOAEC to NOAEC.

*Table 6 Summary of NOAEC/LOAECs from studies, with HECs calculated for different options of lung surface area and human alveolar clearance rate, **with** post-hoc density correction, for possible use by DECOS as a basis for OEL derivation. Note: assessment factors for extrapolation of LOAEC to NOAEC, and subchronic to chronic exposure are not yet applied (and hence it is difficult to directly compare HECs derived from different studies).*

Lung surface, rat and human:			**0.297 and 57.22 m^2**		**0.41 and 143 m^2**	
Alveolar clearance, humans ($t_{1/2}$):			**400 d**	**255 d**	**400 d**	**255 d**
Material	**Duration**	**NOAEC/ LOAEC**	**HEC (mg/m^3)$**	**HEC (mg/m^3)**	**HEC (mg/m^3)**	**HEC (mg/m^3)**
Toner [Muhle]	Chronic	NOAEC = 1 mg/m^3	0.017	0.027	0.031	0.049
TiO_2 [Muhle]	Chronic	NOAEC = 5 mg/m^3	0.191	0.300	0.346	0.543
CeO_2 [EPA]	Subchronic #	NOAEC = 5 mg/m^3	0.065	0.103	0.118	0.186
TiO_2 [Bermudez]	Subchronic #	LOAEC = 9.6 mg/m^3 *	0.282	0.443	0.511	0.802
Fe_3O_4 [Pauluhn]	Subchronic #	LOAEC = 4.7 mg/m^3 *	0.140	0.219	0.253	0.397

$ This column contains the values obtained if the calculations of MAK part A are repeated, but using deposition fractions modelled using the latest version of the MPPD model.
# Assessment factor is needed to correct for duration from subchronic to chronic.
* Assessment factor is needed to correct for LOAEC to NOAEC.

RIVM advises using the data from table 5 without post-hoc density correction as explained in section 4.3. RIVM advises selecting a lung surface area for rats and humans that is based on more than a single measurement and using the same method for both rats and humans (section 4.1), hence the 0.41 and 143 m^2 in the third and fourth column of table 5. Choosing an alveolar elimination rate of 400 days versus 255 days (section 4.2), results in a factor of 1.5 difference in HEC values.

5. Conclusion

1) What is RIVM's assessment of both parts of the OEL derivation approach as performed by the MAK Commission?
   RIVM recommends against using part B, because of several problems, including unclear terms in the formula for calculating a generic particle NOAEC, lack of transparency about how the model for clearance works, and a calculation mistake.
2) What is RIVM's assessment of the underlying toxicity studies in the MAK Commission approach?
   The studies on toner and titanium dioxide (TiO_2) supporting part A of the approach are considered of sufficient quality and include long-term exposure (2 years). However, there are some limitations. For example, the constituent size of the toner particles is unknown, though probably above the nano-range. The agglomerate size of the particles is in the respirable range. In the TiO_2 study, only one concentration was tested, while commonly (at least) three concentrations are included to characterize the toxicity, demonstrate a concentration-response and identify a NOAEC (and LOAEC).
3) Which additional toxicity studies on biopersistent respirable dusts based on a selection made by the DECOS are also suitable for OEL derivation?
   The Part A based OEL approach is strengthened by adding more information from rat inhalation studies on other types of biopersistent respirable dust, as selected by DECOS. However, each additional study has its own strengths and weaknesses.

In two out of three studies, data comes from shorter-duration studies and/or from concentrations where effects were already seen at the lowest concentration (LOAECs), which makes the OEL starting point (HEC) less certain. In the third study (on CeO_2), a less sensitive method was used to assess inflammation compared to the other studies. Still, these studies cover a range of respirable dusts with different densities (1.2 to 7.65 g/cm^3) and particle sizes (MMAD of 1.1 – 4.0 µm).

4) What would the Human Equivalent Concentration (HEC) be if a similar derivation was performed as done by the MAK Commission, but using the latest version of the Multiple-Path Particle Dosimetry (MPPD) model for the alveolar deposition fraction?
   The developers of the particle deposition model MPPD updated their software. When the latest version is used to calculate how much of the particles reach the alveoli (deep lung) in part A's formula, the starting point for setting the OEL based on toner becomes lower, while the starting point based on TiO_2 remains almost the same.
5) What are the HECs from the additional studies using part A of the MAK approach and the latest version of the MPPD model?
   HECs for additional materials were also calculated based on part A using the new version of the MPPD model. This produced a table of starting values, to be used at DECOS discretion as a basis to set an OEL for respirable dust.
6) What is RIVM's assessment of factors that influence the derivation of the OEL in part A?
   There are several uncertainties in calculating the HEC as starting point for the OEL derivation. Some are due to limited amount of inhalation toxicity data for applying part A (as mentioned in answer 3). Other uncertainties come from factors used to adjust from animal to human exposure. RIVM has provided an overview of starting points based on different choices in animal-to-human adjustment factors to clarify these uncertainties.

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Appendix: Modelling of deposition in the lungs using MPPD version 3.04

Table 7: Supplementary MPPD settings

MPPD v3.04 menu	Rat	Human
Input Data – Airway Morphometry		
- Species	Rat	Human
- Model	Asymm. MultiPath Long-Evans	Yeh / Schum 5-Lobe
- FRC (ml)	4.0	3300
- URT (ml)	0.42	50
Input Data – Inhalant Properties		
- Density (g/cm^3)	Study data	Study data (rat)
- Aspect Ratio	1.0	1.0
- Diameter (µm)	Study data	Study data (rat)
- Single / Multiple / Multimodal	Single	Single
- MMAD	Select	Select
- Inhalability Adjustment	Check	Check
- GSD (diam.)	Study data	Study data (rat)
- GSD (length)	1.0	1.0
- Correlation	0.0	0.0
- Equiv. Diam. Model	Unchecked	Unchecked
- Diff. Diameter (µm)	1.0	1.0
- Sed. Diameter (µm)	1.0	1.0
- Imp. Diameter (µm)	1.0	1.0
- Int. Diameter (µm)	1.0	1.0
Input Data – Exposure Condition	Constant Exposure	Constant Exposure
- Acceleration of Gravity (cm/s^2)	981.0	981.0
- Body Orientation	Upright	Upright
- Aerosol Concentration (mg/m^3)	Study data (NOAEC/LOAEC)	Study data (NOAEC/LOAEC)
- Breathing Frequency (/min)	102	20
- Tidal Volume (ml)	2.1	1040
- Inspiratory Fraction	0.5	0.5
- Pause Fraction	0	0
- Breathing Scenario	Nose Only or Whole Body Exposure)	Oronasal-Normal Augmenter
Input Data – Deposition/ Clearance	Deposition only	Deposition only
Plot Results		
- Regional Deposition	Regional Fraction, Whole lung	Regional Fraction, Whole lung
	Deposition fraction in lung is value given for P-region	*Deposition fraction in lung is value given for P-region*
- File	Save Plot and Data	Save Plot and Data

FRC: functional residual capacity; URT: upper respiratory tract volume

Table 8: Pulmonary deposition fraction (P-fraction) modelled using MPPD v3.04

Material	P-fraction rat	P-fraction human
Toner (Muhle, 1991)	0.0064	0.0744
TiO_2 (Muhle, 1991)	0.0711	0.1046
TiO_2 (Bermudez, 2002)	0.0556	0.1064
Fe_3O_4 (Pauluhn, 2011a)	0.0604	0.1068
CeO_2 (US EPA, 2009)	0.0442	0.1070