# uranium (natural), soluble & insoluble compounds (as U)

| CAS number: | 7440-61-1 |
| --- | --- |
| Synonyms: | Depleted uranium, natural uranium, yellowcake |
| Chemical formula: | U |
| Structural formula: | — |

Workplace exposure standard (amended)

| TWA: | **0.2 mg/m3** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **—** |
| Notations: | **—** |
| IDLH: | **10 mg U/m3** |
| **Sampling and analysis:** The recommended value is quantifiable through available sampling and analysis techniques. | |

## Recommendation and basis for workplace exposure standard

A TWA of 0.2 mg/m3 is recommended to protect for kidney damage in exposed workers.

Insufficient data are available to recommend a STEL.

A priority review of the carcinogenic potential for the chemical in the next scheduled review of the workplace exposure standards is recommended.

## Discussion and conclusions

Uranium is used in electric power generation and in the production of paints and certain ammunition.

The critical effect of exposure is kidney damage.

Most human exposure data are confounded by mixed exposures or inadequately designed studies to detect small incidences of adverse effects from chronic exposure (ACGIH, 2018; HCOTN, 2002). The development of critical symptoms depends greatly on the solubility of the material (DFG, 2014). Soluble compounds are absorbed and excreted rapidly and contribute to renal toxicity. Kidney concentrations of 3 µg/g in animals and humans are not associated with adverse effects (ACGIH, 2018; HCOTN, 2002). Insoluble compounds accumulate in the lungs and may cause lung cancer in exposed workers by production of excess reactive oxygen species (ROS) or chronic radiologic effects (DFG, 2014). Epidemiological evidence for such carcinogenic activity is equivocal and the available animal data are inadequate to conclusively evaluate carcinogenicity (HCOTN, 2002).

ACGIH (2018) recommends a TLV-TWA of 0.2 mg/m3. The derivation of TLV-TWA by ACGIH is not detailed but is likely based on the absence of adverse effects at kidney concentrations of 3 µg/g in humans and animals (HCOTN, 2002). This value is supported by industrial observations that there is no increased incidence of adverse effects in exposed workers during a 25-year period of its implementation (ACGIH, 2018). HCOTN also adopted this value of 0.2 mg/m3 as an administrative OEL but is under reconsideration (HCOTN, 2002). A MAK is not assigned by DFG (2014) due to the carcinogenic potential of the substance. However, there is uncertainty in the interpretation of these results with respect to carcinogenicity classification.

In the absence of further information, the TWA of 0.2 mg/m3 by ACGIH (2018) is recommended to be retained. There is insufficient evidence to suggest an immediately acute effect at concentrations within ten times of the recommended TWA. Consequently, the previous STEL of 0.6 mg/m3 is recommended to be withdrawn.

The recommendation of a carcinogenicity notation is disputed in the available source material. Both ACGIH (2018) and DFG (2014) recommend a carcinogenicity notation based on the results of epidemiological studies, but HCOTN (2002) interprets the results of these studies as inconclusive. In view of this uncertainty, further assessment of carcinogenic potential from additional sources is recommended as a priority during subsequent reviews.

## Recommendation for notations

Not classified as a carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). However, there are inconsistencies in the carcinogenicity notation recommendations in the available source material (ACGIH, 2018; DFG, 2014; HCOTN, 2002).

Not classified as a skin sensitiser or respiratory sensitiser according to the GHS.

A skin notation is not recommended based on the available evidence.

# Appendix

### Primary sources with reports

| Source Year set Standard |
| --- |
| SWA 1991 TWA: 0.2 mg/m3; STEL: 0.6 mg/m3 | |
|  |
| ACGIH 2001 TLV-TWA: 0.2 mg/m3 (as U); TLV-STEL: 0.6 mg/m3 (as U) |
| TLV-TWA and TLV-STEL intended to protect for kidney damage and adverse haemopoietic changes, e.g. leukaemia. Substantial evidence for carcinogenicity in humans to assign a carcinogenic notation of confirmed human carcinogen, classification (A1). All exposure routes should be carefully controlled.  Summary of information:  Kidney is the target organ for acutely toxic doses in humans and animals. TLV-TWA recommendation based on lack of evidence for renal or haemopoietic injury at chronic workplace exposures above 0.05 mg/m3 and under 0.2 mg/m3 during 25 years of the implementation of this value; the TLV-STEL is similarly justified with industrial experience indicating limiting acute exposures to 0.6 mg/m3 is protective of critical effects in workers (no further justification provided).  Human data:   * No quantitative dermal BA data available but reports of dermal absorption from occupational exposure are available (no further details provided). Based on analogy to other metals, dermal uptake is considered negligible compared to inhalational uptake * Intestinal absorption rate reported between 0.01–34%, but commonly considered to be ≈1% (no further details provided):   + fasted volunteers absorbed 0.3–3.3% of 10.8 mg of oral dose * ADME data complicated by varying solubilities of different uranium compounds, which are not always specified in the available data:   + pulmonary absorption of 20% reported in an acute inhalational dose, 10–30% reversibly binds to bone, 10–20% deposits in kidneys and 60–70% excreted in urine within 24 h (substance not specified)   + kidney elimination t½ 2–6 d   + 60% of chronic inhalational dose remained in body for 32 d (no further details) * Average elimination t½ of 250 d calculated from workplace study of nuclear fuel workers exposed to uranium dioxide (UO2) at 7 µg/m3 for several years; authors of cited article conclude effective dose at 0.13 mg/m3 corresponds to 0.42 Sv/yr, which is the maximally permissible yearly radiation dose for pulmonary tissue in the absence of other radiation exposure * No excess lung cancer and pulmonary fibrosis attributable to pulmonary uranium concentrations reported in several epidemiological studies of miners. Co-exposure to arsenic, radon, diesel engine fumes, cigarette smoke and silicates likely caused observed excess disease * Occupational exposures prior to 1950 typically 4–30-fold <0.05 mg/m3 (TLV-TWA at the time) in several plants, no abnormal clinical findings reported in workplace review of one such workplace or in 25-yr follow-up study of 3 workplaces (n=100 each).   Animal data:   * Oral LD50 of 1–2 mg/kg (dogs, rats); mice less susceptible (no further details provided) * Substantial damage (not specified) at kidney uranium concentration of 3 µg/g (rodents), proteinuria at 2 µg/g (rats) and threshold for acute renal injury of 0.3 µg/g (dogs) * Reversible kidney damage at 60–240 µg/kg in sub-chronic oral study; cumulative doses 0.66–1.32 mg/kg (rats, 24 d); effects reversible within 35 d * Large brief exposure or chronic exposure to inhalable UO2 dust caused retention in lungs and pulmonary lymph nodes with little translocation to bone or kidney (no further details provided) * Pulmonary fibrosis and malignant neoplasia at 25 mg/m3 in chronic inhalation study (rats, dogs, monkeys, duration and frequency not specified); neoplasia due to alpha radiation * Mild renal injury in some animals at 0.05 mg/m3 (dogs, 1 yr, exposure frequency not specified); steady state renal uranium concentration reported at 0.3–0.4 µg/L.   Insufficient data to recommend notations for skin absorption and sensitisation. |
| DFG 2014 not assigned |
| Summary of additional information:  Kidneys are target organs for soluble compounds, lungs for insoluble compounds. Toxicity considered to act via multiple mechanisms, including disruption of calcium homeostasis, generation of ROS from redox reactions with glutathione and radioactivity. MAK not established due to carcinogenicity of uranium compounds in humans and animals; insoluble and soluble compounds assigned to category 2 and category 3B, respectively.  *Carcinogenicity*   * Epidemiological data confounded by co-exposures, but indicate association between insoluble uranium exposure and excess lung cancer in workers, supported by carcinogenicity in chronic inhalation studies in dogs (category 2) * Soluble uranium compounds are suspected carcinogens (category 3B) based on limited animal carcinogenicity data and analogy to carcinogenicity of insoluble compounds.   *Radioactivity*  Based on protection for excess radiation alone (i.e. ≤0.02 Sv/yr or 0.4 Sv/40-yr working lifetime recommended by German Commission on Radiological Protection), threshold values of 0.25 mg/m3 and 0.025 mg/m3 for soluble and insoluble compounds are recommended, respectively. DFG emphasises values are not protective of nephrotoxicity and do not constitute a MAK.  A skin notation is recommended based on evidence for systemic effects following dermal application of both soluble and insoluble compounds in rabbits.  MAK derivations of insoluble and soluble compounds are reported but are not recommended by the agency.  *Insoluble uranium compounds*  A MAK of 0.0005 mg/m3 for insoluble uranium compounds would increase radiation exposure in the lung by a factor of 2 above background based on the general threshold for insoluble dust and background radiation exposure of 1.1 mSv/yr in German populations.  *Soluble uranium compounds*  A benchmark calculation for a 5% increase in incidence of nephrotoxicity corresponds to 0.025 mg/m3 based on the dose-response relationship for renal damage in dogs chronically exposed to soluble uranium (uranium hexafluoride and uranium tetrachloride). A MAK of 0.01 mg/m3 based on this benchmark dose would contribute an additional 0.2 mSv/yr in the lungs for a particle size of 5 µm.  Human data:   * Available epidemiological data inconclusive regarding an association between occupational exposure to poorly soluble compounds and kidney damage in milling operations and munitions production/handling (depleted uranium) (no details on exposure are provided):   + a cited article assumes that renal uranium concentrations of 2–3 µg/g are not toxic, but this effect level is not confirmed in the available database * Non-sensitising in patch test of workers (n=175), 36 of whom had contact dermatitis * Results of several epidemiological studies of mining, processing and enrichment workers are summarised, these studies give inconclusive evidence for carcinogenicity in humans:   + significant increases in mortality from lung cancer in exposed workers   + studies are confounded by mixed exposures to other airborne contaminants and radiation sources * Increased chromosomal aberrations in lymphocytes in exposed mining, processing and military workers; no increased frequency in chromosomal aberrations in workers exposed to uranium that produced radiation at 0.25–0.5 mSv.   Animal data:   * Dermal flux *in vitro* 22.36 ng/cm2/h (rats), 31.17 ng/cm2/h (pigs) * LOAEC of 0.05 mg/m3 for mild kidney tubule damage in chronic inhalation study using soluble uranium hexafluoride (dogs, 6 h/d, 5/5 d/wk, 1 yr). Effects more severe at 0.2 mg/m3 * DFG considers the available evidence for carcinogenicity in animals inconclusive due to inadequate experimental designs:   + increased incidence of lung and lymph node tumours and pulmonary fibrosis in 2 chronic inhalation studies using UO2 (dogs, monkeys, 1–5 yr); all animals were exposed at 5.8 mg/m3, duration and frequency were adjusted to produce cumulative radiation doses between 7–132 Sv (lungs) and 26–3,200 Sv (lymph nodes)   + no increased tumorigenicity at 0.15–0.25 mg/m3 (1st yr) and 2 mg/m3 (2nd yr) using uranyl nitrate (rats, dogs, 2 yr); similar dose regimens using other soluble uranium compounds at 0.2–10 mg/m3 also did not elicit increased tumorigenicity * Soluble compounds are genotoxic *in vitro* in bacteria mammalian cells due to formation of DNA adducts, DNA strand breaks, micronucleus formation and gene mutations; genotoxic *in vivo* due to increased sperm abnormalities and micronucleus formation in bone marrow at 4 and 40 mg/kg (mice):   + authors of cited articles conclude effects due to radiation are negligible * Insoluble compounds caused gene mutation and micronuclei *in vitro* in bacteria and DNA damage in kidneys *in vivo* following acute inhalation of 190 mg/m3 or 375 mg/m3 insoluble UO2 (rats, 30 min); these effects were likely due to formation of ROS during metabolism rather than radioactivity, because depleted uranium was used in these studies. |
| SCOEL NA NA |
| No report. |
| OARS/AIHA NA NA |
| No report. |
| HCOTN 2002 TWA: 0.2 mg/m3 |
| Summary of additional information:  Available report is an overview of the health risks of exposure to depleted uranium and contains some information on occupational exposure to naturally occurring uranium. Existing administrative OEL of 0.2 mg/m3 (TWA) for natural uranium adopted from ACGIH (1976) TLV recommendation, but provisionally considered too high. A health-based recommended OEL (HBROEL) is not derived.   * Origin of ACGIH (1976) TLV-TWA unclear. HCOTN assumes it is based on tissue concentrations not associated with increased radiological risk or adverse kidney effects as observed in animals:   + kidney concentration of 3 µg/g cited as level of accumulation without serious adverse effects in animals   + in humans, kidney concentrations of 2–6 µg/g had no serious impact on health   + generally accepted safe level of 3 µg/g is thus recommended by consensus rather than health-based evidence * It may be inferred from evidence for kidney damage at kidney concentrations of 0.1–0.4 µg/g in animals (no further details) that a conventional threshold of 3 µg/g should be provisionally reduced by an order of magnitude pending further assessment * The following occupational radiation exposure dependent on solubility and activity median aerodynamic diameter (AMAD) of the particles reported for 1 yr at the TLV ≡53 (insoluble) or 3.6 mSv (soluble) with 1 µm AMAD or 41 (insoluble) or 4.3 mSv (soluble) with 5 µm AMAD:   + radiological effects are critical effects for insoluble compounds; exposure limited by radiological protection requirement of 20 mSv/yr   + air concentration of insoluble particles corresponds to an effective radiation dose of 20 mSv/yr ≡75 µg/m3 (1 µm AMAD) or 96 µg/m3 (5 µm AMAD)   + for soluble compounds, the TLV of 200 µg/m3 is applicable to protect for potential kidney damage, since radiological effects are not expected * Epidemiological evidence from 2 studies may be inferred to suggest inhalational exposure not associated with increased risk of lung cancer at an absorbed radiation dose <200 mGy. Evidence for lung cancer above this level is inconclusive * Radioactivity of natural and depleted uranium is low’. Carcinogenicity due to radiological effects therefore anticipated to be undetectable in the available human and animal dataset, but potential carcinogenicity is not ruled out by analogy to carcinogenicity from other sources of radiation:   + exposure to a radiation dose of 1 mSv corresponds to an increased cancer risk of 5 in 100,000, which is currently the individual dose limit for the general public   + occupational equivalent is 20 mSv/yr * Acute exposure to >1 mg uranium induced acute, but generally reversible, kidney dysfunction (no further details provided) * No dose-related change kidney disease incidence in populations with chronic exposure to natural uranium, e.g. mining and military workers:   + lack of reports of kidney damage in available human database suggests current occupational exposure concentrations are not toxic. |

### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| IARC |  | 1999 | * Available report assesses carcinogenicity of implanted uranium metal only (primarily depleted uranium from ammunition/shrapnel fragments) * Regardless of exposure route, most absorbed uranium is excreted in urine within 24 h:   + retained substance reabsorbed in kidneys, where it causes its primary toxic effects   + chronically exposed uranium mill workers showed mild dysfunction of the kidney * Implanted uranium not classifiable as human carcinogen (Group 3). |
| US NIOSH |  | 1994 | * IDLH for soluble uranium compounds based on chronic toxicity data in animals * IDLH for insoluble compounds based on sub-chronic inhalation toxicity data in animals and to be consistent with soluble uranium compounds. |

### Carcinogenicity — non-threshold based genotoxic carcinogens

| Is the chemical mutagenic? | Yes |
| --- | --- |
| Is the chemical carcinogenic with a mutagenic mechanism of action? | Insufficient data |
| **Insufficient data are available to determine if the chemical is a non-threshold based genotoxic carcinogen.** |  |

## Notations

| Source | Notations |
| --- | --- |
| SWA | — |
| HCIS | — |
| NICNAS | NA |
| EU Annex | — |
| ECHA | — |
| ACGIH | Carcinogenicity – A1 |
| DFG | Carcinogenicity – 2, H (skin) |
| SCOEL | NA |
| HCOTN | — |
| IARC | — |
| US NIOSH | NA |

NA = not applicable (a recommendation has not been made by this Agency); — = the Agency has assessed available data for this chemical but has not recommended any notations

### Skin notation assessment

| Calculation |
| --- |
| |  |  |  |  | | --- | --- | --- | --- | | Adverse effects in human case study: |  |  |  | | Dermal LD50 ≤1000 mg/kg: |  |  |  | | Dermal repeat-dose NOAEL ≤200 mg/kg: |  |  |  | | Dermal LD50/Inhalation LD50 <10: |  |  |  | | *In vivo* dermal absorption rate >10%: |  |  |  | | Estimated dermal exposure at WES >10%: | no | -2.00 |  | |  |  | -2 | **a skin notation is not warranted** | |

### IDLH

| Is there a suitable IDLH value available? | Yes |
| --- | --- |

## Additional information

| Molecular weight: | 238.03 |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = 9.76 mg/m3; 1 mg/m3 = 0.10 ppm |
| This chemical is used as a pesticide: |  |
| This chemical is a biological product: |  |
| This chemical is a by-product of a process: |  |
| A biological exposure index has been recommended by these agencies: | ACGIH  DFG  SCOEL |

## Workplace exposure standard history

| Year | Standard |
| --- | --- |
| Click here to enter year |  |

## References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7th Edition Documentation, CD-ROM, Single User Version. Copyright 2018. Reprinted with permission. See the [*TLVs® and BEIs® Guidelines section*](http://www.acgih.org/tlv-bei-guidelines/policies-procedures-presentations) on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2014) Substance Overview for Uranium and its hardly soluble inorganic compounds – MAK value documentation.

Health Council of the Netherlands (HCOTN) (2002) Health risks of exposure to depleted uranium, an overview. The Hague: Health Council of the Netherlands; publication no. 2001/13E.

International Agency for Research on Cancer (IARC) (1999) Surgical implants and other foreign bodies. IARC Monographs – 74.

Tenth Adaptation to Technical Progress Commission Regulation (EU) No 2017/776 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (the CLP Regulation).

US National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to life or health concentrations – uranium (insoluble compounds, as U).

US National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to life or health concentrations – uranium (soluble compounds, as U).