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Agreed

APPLICATION FOR AUTHORISATION: ESTABLISHING A REFERENCE DOSE RESPONSE RELATIONSHIP FOR CARCINOGENICITY OF MOCA

Background

At the 22nd meeting of the Committee for Risk Assessment (RAC) in September 2012, the ECHA Secretariat presented a proposal to set DNELs/DMELs and dose response relationships for substances prior to receiving applications for authorisation (AfAs). This was initially approved by RAC as a trial exercise. However, in early 2015, ECHA agreed to continue supporting the practise for Annex XIV substances, recognising its value to the Authorisation process and its efficiency[1].

The DNELs/DMELs and dose response relationships so derived will serve as a non-legally binding 'reference value'. They provide applicants with a clear signal as to how RAC is likely to evaluate these important elements of the risk assessment of AfA.

This initiative is intended to improve the efficiency of the AfA process as a whole by discussing and when possible publishing reference values such as DNEL's or dose response relationships in advance of applications, so providing greater consistency and better use of the legally defined periods of opinion-development in the RAC.

Requested action:

Following the Committee's agreement on the document, it will be published on the ECHA website.

Annex 1: Reference dose response relationship for carcinogenicity of MOCA

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[1] At the Conference on "Lessons learnt on Applications for Authorisation" co-organised by ECHA and the European Commission that took place on 10-11 February 2015.

Annex 1 Reference dose response relationship for carcinogenicity of MOCA
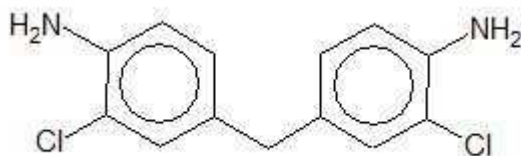
2,2'-Dichloro-4,4'-methylenedianiline (MOCA, CAS RN: 101-14-4; EC Number: 202-918-9) is included in Annex XIV of REACH "List of substances subject to authorisation".

Relevance of endpoints

For applicants applying for authorisation under Article 60(2) (adequate control route), in order to conclude whether adequate control is demonstrated, only endpoints (i.e. properties of concern) for which the substance is included in Annex XIV need to be addressed in the hazard assessment[1]. However, information on other endpoints might be necessary for comparing the risks with the alternatives.

For applicants aiming at authorisation based on Article 60(4) (socio-economic analysis route) Article 62(4)(d) also applies and the socio-economic analysis (SEA) route will as a consequence focus on the risks that are related to the intrinsic properties specified in Annex XIV. The SEA should in turn consider the impacts related to such risks. In practice the applicant is expected to provide this information in their Chemical Safety Report (CSR) for which an update may be advisable. However, for an authorisation to be granted, the applicant should also demonstrate that there are no suitable alternatives. In this latter analysis it may be the case that other endpoints than those for which the substance was listed in 'Annex XIV' become relevant in order to demonstrate that no suitable alternative is available.

MOCA was included on Annex XIV due to its carcinogenic properties. The reference dose response relationships proposed in the present document are only based on carcinogenicity arising from MOCA exposure[2].

Carcinogenicity

Table 1 below provides an overview of expert assessments on the carcinogenic mode of action, the assumed carcinogenic mechanism and the low-dose extrapolation approaches that were used:

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[1] Article 60(2) states "…an authorisation shall be granted if the risk to human health or the environment from the use of the substance arising from **intrinsic properties specified in Annex XIV** is adequately controlled."

[2] Endpoints relevant to the authorisation are also discussed in section 5 of the document: "How RAC and SEAC intend to evaluate the applications" (common approach of RAC and SEAC in opinion development on applications for authorisation, agreed RAC-20/SEAC14, 24/03/2012). Link: http://echa.europa.eu/web/guest/applying-for-authorisation/additional-information

Table 1 Overview of the findings of Expert assessments on the carcinogenic mode of action of MOCA

Expert evaluation	Primary mechanism	Threshold/non-threshold approach	Studies	Threshold dose
IARC (2010)	Genotoxic mechanism: • metabolic activation to *N*-hydroxy MOCA	Not addressed	Inadequate evidence in humans of carcinogenicity sufficient evidence in experimental animals of carcinogenicity – the main target tissues: • liver and lungs in rats • urinary bladder in dogs	not addressed
IARC (2012)	Genotoxic mechanism: metabolic activation *N*-oxidation in the liver *O*-acetylation in the bladder	Not addressed	Inadequate evidence in humans of the carcinogenicity of MOCA sufficient evidence in experimental animals of the carcinogenicity of MOCA	not addressed
ATSDR (1994)	Not reported	Not addressed	Reported to be a suspected bladder carcinogen considered a probable human carcinogen	not addressed
Chemtura Belgium N.V., 2014; Limburge Urethane Casting N.V., 2010	Genotoxic mechanism	Non-threshold	Lung, mammary, zymbal gland and liver tumours detected in an 18-month study in male rats (Kommineni *et al*., 1979)	**WORKERS:** **dermal:** BMDL10 = 178 mg/kg bw/day AF = 40 000 DMEL = 4.45 x 10^{-3} mg/kg bw/day **inhalation:** BMCL10 = 7.76 mg/m^3 SF = 10 000 DMEL = 7.76 x 10^{-4} mg/m^3

Expert evaluation	Primary mechanism	Threshold/non-threshold approach	Studies	Threshold dose
Chemtura Belgium N.V., 2014; Limburge Urethane Casting N.V., 2010	Genotoxic mechanism	non-threshold	lung, mammary, zymbal gland and liver tumours detected in an 18-month study in male rats (Kommineni *et al*., 1979)	**GENERAL POPULATION:** **dermal:** $BMDL10 = 178$ mg/kg bw/day $SF = 40\ 000$ $DMEL = 4.45 \times 10^{-3}$ mg/kg bw/day **inhalation:** $BMCL10 = 3.07$ mg/m^3 $SF = 10\ 000$ $DMEL = 3.07 \times 10^{-4}$ mg/m^3 **oral:** $BMDL10 = 4.44$ mg/kg bw/day $SF = 40\ 000$ $DMEL = 1.11 \times 10^{-4}$ mg/kg bw/day
DECOS, 2000	Genotoxic mechanism	Non-threshold	DECOS assessed all the studies for additional lifetime cancer risk associated with occupational exposure. Different methodology using malignant tumours to calculate incidence/mg/kg bw/day.	Results varied from 2.2×10^{-3} to highest incidence 3.7×10^{-2}/mg/kg bw/day (Grundmann and Steinhoff, 1970) Corresponds to additional lifetime cancer risk of 4×10^{-5} for 40 y exposure to 0.02 mg/m^3

BMCL10: Lower 95% confidence limit of a benchmark concentration representing a 10% tumour response following lifetime exposure.

BMDL10: Lower 95% confidence limit of a benchmark dose representing a 10% tumour response following lifetime exposure.

DMEL: Derived Minimum Effect Level.

SF: Safety Factor (Assessment Factor).

Mechanism of action

The precise mechanism of action for carcinogenicity of MOCA is not fully understood; however, MOCA has the potential to form adducts with DNA. (ATSDR, 1994; IARC, 2012). The reactive nitrenium ion was identified as reacting primarily with C8-deoxyadenosine in rats (Beland and Kadlubar, 1990; IARC, 2010; IARC, 2012; Swaminathan *et al.*, 1996). These MOCA-DNA adducts have been reported in urothelial cells of an exposed worker; liver, kidney, lung and bladder of rat and dog in *in vivo* studies (IARC, 2012; Swaminathan *et al.*, 1996).

As well as forming MOCA-DNA adducts, data suggest that MOCA can also react and generate adducts with haemoglobin and serum albumin (Cheever *et al.*, 1988, 1990, 1991; Vaughan and Kenyon, 1996).

Genotoxicity

IARC (2010, 2012) reported strong evidence of the carcinogenicity of MOCA via a genotoxic mechanism of action. The data suggest that the genotoxic mechanism includes metabolic activation of MOCA to form adducts with DNA, resulting in the induction of mutagenic and clastogenic effects in humans.

The data suggest that MOCA is mutagenic in several strains of *Salmonella typhimurium* tested with metabolic activation in the Ames assay. The genotoxic assays conducted in several strains of *Saccharomyces cerevisiae* indicate that MOCA is not genotoxic in these test systems. MOCA induced chromosomal aberrations (including single DNA strand breaks) either with or without metabolic activation, and unscheduled DNA synthesis without activation. The mouse lymphoma assay identified both positive and negative results with and without metabolic activation, respectively. The available *in vivo* data strongly suggest that MOCA is genotoxic in experimental animals following dermal, inhalation and oral exposure. MOCA induced DNA adduct formation in two species of rat following oral, dermal and intraperitoneal injection. MOCA also induced micronuclei in B6C3F1 mice via intraperitoneal injection; however, it did not induce micronuclei via the same exposure route in CD-1 mice.

The weight of evidence from the genotoxicity data, particularly the *in vivo* studies, indicates that it should be considered a genotoxic agent.

Animal studies

IARC classified MOCA as Group 2B (possibly carcinogenic to humans) because, while there is strong evidence of carcinogenicity in animals, there was no convincing evidence in humans (IARC, 2010, 2012).

There have been a number of carcinogenicity studies with MOCA although they are all rather old and conducted before the modern guidelines and GLP were implemented. These are outlined in Table 2. Although these studies in rats suffer from a limited range of doses and exposure times, and some experienced high mortality rates, they consistently show an increased incidence of lung and liver tumours.

Table 2   Overview of the chronic carcinogenicity studies of MOCA

Reference	Study details	Dose	Findings
Russfield *et al.* (1975)	• HaM/ICR mice M/F • 25/sex/dose • 18 months exposure and 6 months observation • oral exposure via diet	• 0, 130 or 260 mg/kg bw/day MOCA hydrochloride salt (purity 97%)	• significant increase in incidence of hepatomas in both dose groups of F
Grundmann and Steinhoff (1970)	• Wistar rats M/F • 25/sex/dose and 50/sex controls • 500 days and observation period (lifetime) • oral exposure via protein-deficient diet	• 0 or 54 mg/kg bw/day MOCA (purity unspecified)	• significant increase in hepatomas and lung tumours in M & F • high mortality rate in M & F
Russfield *et al.* (1975)	• Charles River CD-1 rats M • 25/dose • 18 months exposure and 6 months observation • oral exposure via standard protein diet	• 0, 25 or 50 mg/kg bw/day MOCA hydrochloride salt (purity 97%)	• no significant increase in tumours
Stula *et al.* (1975)	• Charles River CD rats M/F • 50/sex/dose • 2 years • oral exposure via a standard-protein diet (23% protein) • 6/dose sacrificed for a one-year interim evaluation	• 0 or 50 mg/kg bw/day MOCA (purity ~95%)	• significant increase in lung adenomatosis (pre-neoplastic lesion) and lung adenomatosis in M & F
Stula *et al.* (1975)	• Charles River CD rats M/F • 25/sex/dose • 16 months • oral exposure via a low-protein diet (7%) • 6/dose sacrificed for a one-	• 0 or 50 mg/kg bw/day MOCA (purity ~95%)	• significant increase in lung adenocarcinomas and lung adenomatosis in M & F • significant increase in hepatocellular carcinomas and hepatocellular adenomas in M

Reference	Study details	Dose	Findings
	year interim evaluation		• significant increase in mammary gland adenocarcinomas in F
Kommineni *et al*. (1979)	• Charles River Sprague-Dawley rats M • 100 rats (control and low-dose group), 75 rats (mid-dose group) and 50 rats (high-dose group) • 18 months exposure and 6 months on diet and 32 weeks observation • **Group A**: ○ protein-adequate diet (27%) • **Group B**: ○ a protein-deficient diet (8%)	**Group A (male rats)**: Dietary levels - 0, 250, 500, 1000 ppm (12.5, 25 or 50 mg/kg bw/day) MOCA (industrial grade) **Group B**: Dietary levels – 0, 125, 250, 500 ppm (0, 6.25, 12.5 and 25 mg/kg bw/day) MOCA	• significant increase in lung adenocarcinomas, all lung tumours, mammary gland adenocarcinomas, Zymbal gland carcinomas, hepatocellular carcinomas and haemangiosarcomas
Stula *et al*. (1978)	• Beagle dogs F • 6/dose • 3 days/week for 6 weeks, then 5 days/week for 9 years • oral exposure	• 100 mg MOCA (~90% purity) in a gelatine capsule (average 10 mg/kg bw/day)	• Urinary bladder transitional cell carcinomas were reported in 4/5 (80%) of the treated female dogs The other treated dog died early, not related to treatment.
Steinhoff and Grundmann (1969)	• Wistar rats M/F • 17/sex/dose and 25/sex controls • 88 weeks exposure and 23 weeks observation (lifetime) • subcutaneous injection	• 0, 500 or 1000 mg/kg bw MOCA (94% purity)	• significant increase in hepatocellular carcinomas and lung cancers

F: Female.

M: Male.

There is an oral long-term (up to 9 years) study in Beagle dogs with a single dose in which bladder tumours were observed in 4 out of 5 surviving treated dogs. This result, together with the epidemiological studies, indicates weak evidence that bladder cancer may be associated with MOCA exposure (Stula *et al*., 1978). Due to the limited number of animals the study is not however, suitable for risk assessment. The most-complete dose-response study, although with high mortality, is that of Kommineni *et al.* (1979) in which rats with an adequate protein diet (a further treated group had inadequate protein) were treated orally. The use of T25 in the cancer risk estimates using lower dose tumour incidences counters this higher mortality in the study. This study was used for risk assessment in the Chemical Safety Reports (CSRs: Chemtura, 2014; Limburge Urethane Casting N.V., 2010).

In the Dutch DECOS (2000) assessment of the long-term carcinogenicity studies, the Kommineni *et al*. (1979) study had an incidence of tumours of 3.5×10^{-2}/mg kg bw/day, close to the highest incidence of 3.7×10^{-2}/mg/kg bw/day (Grundmann and Steinhoff, 1970). This assessment, while giving some indication of the comparative sensitivity of the carcinogenicity studies, uses different methodologies to those REACH Guidance methods used in this risk assessment and so the tumour frequencies are not suitable.

The frequency of combined lung tumours observed in the Charles River CD rat oral long-term study of Kommineni *et al.* (1979) will be used in this review to derive lifetime cancer risk estimates. In the part of the study to be used, male rats were exposed to industrial grade MOCA (unspecified purity) in protein-sufficient diets (27% protein; a further group had a protein-restricted diet, 8% protein) at 0, 250, 500 and 1000 ppm for 18 months following by a 6-month recovery period. This corresponded to a received dose of 0, 12.5, 25 and 50 mg/kg bw/day estimated by assuming that a rat consumes 5% of its body weight per day (US EPA, 2006). These doses were expanded to continuous lifetime exposure by multiplying by 18/24 months to give a corrected dose (US EPA, 2006). Tumours were detected in the lung, mammary gland, Zymbal gland and liver. Combined lung tumours (adenomas, epidermoid carcinomas and adenocarcinomas) gave the most complete dose response data, and lung tumours are the most frequently observed tumours seen in the experimental animal long-term studies. The tumour incidence is shown in Table 3 below.

Table 3 Lung tumour incidence in Male rats (Kommineni *et al,* 1979)

Dietary Dose (ppm)	0	250	500	1000
Dose/animal (mg/kg bw/day	0	12.5	25	50
Corrected Dose (mg/kg bw/day)	0	9.4	18.8	37.5
Total Tumours/animals	1/100	23/100	28/75	35/50
Incidence	0.01	0.23	0.37	0.70

Human studies
Four epidemiological studies were located and these mainly concentrated on the possible increased incidence of bladder cancer (Ward *et al*., 1990; Chen *et al*., 2005; Mason *et al*., 1990; Dost *et al*., 2009). This was based on the known properties of other similar amine compounds such as benzidine and naphthylamine. There were US, Taiwan and UK studies following workers exposed to MOCA and monitoring urine samples. There were low levels of bladder cancers and abnormalities in cells in urine detected in these studies but the lack of appropriate controls and exposure to a number of other potentially carcinogenic chemicals and

other confounders means that there is no convincing evidence of a causal association between MOCA exposure and bladder cancer. IARC (2010, 2012) reported that "no adequate epidemiology studies were available to the Working Group to evaluate an association between MOCA and bladder cancer risk".

Bioavailability

Data from occupational studies have identified that the most likely routes of exposure to MOCA are from contact with contaminated surfaces i.e. dermal, followed by inhalation and oral pathways.

No specific studies were located on the absorption of MOCA in humans following oral exposure. The results from rats administered a single oral dose of radiolabelled MOCA via oral gavage suggest that MOCA is partially absorbed following oral exposure. 16.5% MOCA was excreted in urine within 72 hours, 13.7% was retained in the tissue, while approximately 60% remained unabsorbed in faeces (Groth et al., 1984).

Occupational workers exposed to MOCA during its manufacturing process, which can either exist as a liquid emulsion, solid pellets with dust, or as solid pellets without dust (IARC, 2012). NIOSH (1986) reported the concentrations of MOCA in the urine of exposed workers over a period of 22 months and identified the levels of MOCA from 5.3 to 43.8 µg/l. A detailed review of the data identified that the highest MOCA concentrations in urine detected were in workers in direct daily contact with MOCA i.e. mixers and molders.

One study indirectly evaluated the absorption of MOCA in five male factory workers over a 5-day period. MOCA air concentrations were monitored for each worker over 6-7 hours every other day and urinary MOCA concentrations were obtained over the 5 days. MOCA air concentrations ranged from 0.0002 to 0.0089 mg/m^3. The concentration of MOCA detected in urine was greater than the reported air concentrations, identifying that another potential route of MOCA exposure is dermal (Ichikawa et al., 1990).

The differences in absorption rates of radiolabelled MOCA (^{14}C-MOCA) in Beagle dogs following either dermal or intravenous exposures were reported for 24 hours following MOCA administration. Only 2.4% MOCA was reported to be absorbed via dermal administration (Manis et al., 1984). Groth et al. (1984) reported 11.5-21.9% of MOCA absorption in Sprague Dawley rats following 72 hours of dermal application to the skin.

The absorption and penetration of radiolabelled MOCA through 7 x 7 mm area of fresh human neonatal foreskin organ cultures was reported over a four-hour period. One hour following dermal application, 46% of the radiolabelled MOCA was reported on the skin, 0.5% was detected on the underlying membrane, while the remaining 53.5% radiolabelled MOCA was unabsorbed. Four hours after the initial radiolabelled MOCA, 61% was detected in the skin, 26% was detected on the underlying membrane and 12% remained unabsorbed. The authors suggested that MOCA was readily absorbed without being metabolised (Chin et al., 1983).

No additional studies were located on the direct measurement of MOCA absorption in humans or experimental animals via inhalation exposure.

Therefore for the risk estimations, the following absorption values were used:

Oral absorption – no human data and partially absorbed in rats; therefore, an oral absorption of 50% is assumed and when extrapolating from oral to inhalation toxicity a correcting factor of 2 is used according to the REACH Guidance.

Dermal absorption – There are no *in vivo* dermal absorption data in humans, in one

study in rats dermal absorption of 11.5-21.9% is observed and human tissue culture study suggests even higher absorption; 50% default value for dermal absorption is used according to the REACH Guidance.

Inhalation absorption - No studies located – 100% default value according to the REACH Guidance

Carcinogenicity risk assessment

T25 Derivation

The T25 value for MOCA has been derived using information from a long-term study on Charles River CD rats administered MOCA in the diet with adequate protein (Group A) and using the frequency of all lung tumours (adenoma, epidermoid carcinoma and adenocarcinoma) (Table 3; Kommineni *et al*. 1979).

- lowest dose with a significantly increased frequency (C) of 9.4 mg/kg bw/day
- Incidence at C, 0.23
- Control incidence, 0.01

T25 is derived using the following calculation:

C x (Reference incidence 0.25)/(incidence at C – control incidence) x (1-control incidence)/1

$$\text{The lowest } T25_{(oral, rat)} = 9.4 \times 0.25/0.23-0.01 \times 1-0.01/1$$
$$= 10.6 \text{ mg/kg bw/day.}$$

Therefore **$T25_{(oral, rat)}$ = 10.6 mg/kg bw/day**.

This value is used as the PoD for the derivation of route-specific risk estimates for workers and the general population.

Workers

Workers inhalation risk estimate

The $T25_{(oral, rat)}$ was corrected for inhalation exposure assuming 100% absorption and correcting for:
- rat oral intake (mg/kg bw/day) to rat inhalation (0.8 l/min/8 h);0.384 m^3/kg bw/8 h
- oral absorption rat/inhalation humans (50/100)
- activity driven difference for workers (standard respiratory volume for humans, 6.7/respiratory volume in light work for workers,10 m^3)

$T25_{(inhalation, human)}$ = 10.6 x 1/0.384 x 6.7/10 x 50/100 = 9.25 mg/m^3

Correcting for worker exposure:
- workers exposure is 5 day/week, 48 weeks/year, 40 years in an average lifespan of 75 years
- correction factor for workers' exposure of 7/5 x 52/48 x 75/40 = **2.8**

$T25_{(inhalation, workers)}$ = 9.25. mg/m^3 x 2.8 correction factor = 25.9 mg/m^3

Workers dermal risk estimate

Taking the T25$_{(oral, rat)}$ and correcting for
- dermal default exposure of 50% and oral absorption of 50%
- allometric scaling of 4 from rats to humans:

T25$_{(dermal, human)}$ = 10.6/(50/50)/4 = 2.65 mg/kg bw/day

Correcting for workers' exposure as above:

T25$_{(dermal, workers)}$ = 2.65 x 2.8 = 7.4 mg/kg bw/day

General population inhalation risk estimate

T25$_{(oral, rat)}$ 10.6 mg/kg bw/day corrected for general population inhalation exposure:
- allometric scaling from rats to humans, 4,
- human weight 70 kg
- human general population breathing 20 m^3 per person
- default oral absorption (50%) to inhalation absorption (100%).

T25$_{(inhalation, gen pop)}$ = 10.6/4 x 70/20 x 50/100 = 4.6 mg/m^3

General population oral risk estimate

T25$_{(oral, rat)}$ corrected to T25$_{(oral, general pop)}$ by allometric scaling, from rats to humans, 4.

T25$_{(oral, general pop)}$ = 10.6/4 = 2.65 mg/kg bw/day

A summary of the cancer risk estimates is shown in Table 4.

Table 4   Cancer risk estimates for MOCA

Route of exposure	Population	T25 Descriptor	Cancer risk for 1 unit amount
Oral	General population	T25$_{(oral, general pop)}$ 2.65 mg/kg bw/day	**9.43 x 10^{-5} per µg/kg bw/day**
Inhalation	Workers	T25 $_{(inhalation, workers)}$ 25.9 mg/m^3	**9.65 x 10^{-6} per µg/m^3**
	General population	T25$_{(inhalation general pop)}$ 4.6 mg/m^3	**5.43 x 10^{-5} per µg/m^3**
Dermal	Workers	T25$_{(dermal, human)}$ 7.4 mg/kg bw/day	**3.38 x 10^{-5} per µg/kg bw/day**

Assuming linearity of response the cancer risk for lifetime exposure to each unit amount of MOCA will increase in proportion, e.g. for workers' exposure by inhalation

1 µg/m³	**9.65 x 10⁻⁶**
2 µg/m³	**1.93 x 10⁻⁵**
5 µg/m³	**4.83 x 10⁻⁵**
10 µg/m³	**9.65 x 10⁻⁵**

Biomonitoring approach

An additional approach for assessing the exposure and risk of MOCA is the biomonitoring of occupationally exposed workers. This approach has been summarised by SCOEL particularly in the 2013 Annex to its recommendations on MOCA (SCOEL, 2010/2013).

There have been a number of studies measuring MOCA in urine. MOCA is excreted as 'free' MOCA but also as metabolites, glucuronide-MOCA and acetyl-MOCA. Commonly used methods have been developed to measure total MOCA (free and conjugated MOCA) expressed in µmol/l or µmol/mol creatinine (to correct for urinary creatinine excretion). Detection limits vary between 3.7-5 nmol/l (1-1.5 µg/l), corresponding approximately to 0.35-0.5 µmol/mol creatinine (SCOEL, 2010/2013). In workers not exposed to MOCA, urinary levels are below the detection limits of these modern analytical techniques.

Since MOCA is a genotoxic, non-threshold carcinogen, SCOEL has not set any biological limit value for MOCA, but has derived a Biological Guidance Value which typically represents the 95th percentile of the biomarker levels in occupationally non-exposed populations. In the case of MOCA, this is below the detection limit, and so any concentrations detected suggest occupational exposure.

There are no reliable measured data on correlations between urinary MOCA levels and MOCA air concentrations, so it is not possible to directly calculate urinary levels which correspond to occupational exposure, e.g. 1 or 10 µg/m³.

In SCOEL (2010/2013) an open one-compartment model to calculate the daily dose corresponding to urinary MOCA level of 5 µmol/mol creatinine in the Friday afternoon (end of shift) sample (SCOEL 2010/2013) is described. For a substance following first order elimination kinetics the decrease in urinary level follows the formula

$$Ct = Cp \times e^{-t \times kelim}$$

where Ct = concentration at time point t after the peak concentration; Cp = peak concentration, and K_{elim} = elimination rate constant, = $\ln2/T_{1/2}$.

Assuming that the half-time of MOCA is 23 hours and the steady state is reached after one-week exposure, an average urinary concentration of MOCA at steady state is 2.6 µmol/mol creatinine when the concentration in the Friday afternoon sample is 5 µmol/mol creatinine.

Urinary excretion of 5 µmol/mol creatinine in the Friday afternoon can then be calculated to using the formula:

$$D = C_{ss} \times Cr_{24h} \times M/BW \times F_{ue}$$

where D = daily dose (µg), Css = average concentration in the urine, Cr_{24h} = average daily excretion of creatinine for a 50-year old man of 70 kg (12 mmol), Fue = proportion of dose excreted in urine (50% in the case of MOCA).

$$2.6 \text{ µmol/mol creatinine} \times 0.012 \text{ mol} \times 267.17 \text{ g/mol} /0.5 = 17 \text{ µg}$$

SCOEL then used unit cancer risk estimates derived by DECOS (see Table 1) to calculate cancer risk for different urinary MOCA levels. These risk estimates were derived using a different method from that in the REACH Guidance. It should be noted, that SCOEL gave these risk estimates for information only, and did not set any limit value based on these calculations.

The risk estimates derived above using the REACH Guidance can be used to calculate the risk level for different urinary MOCA levels.

Since 1 µg/m^3 exposure (which corresponds to a daily dose of 10 µg in occupational exposure) represents a cancer risk of 9.65×10^{-6},

5 µmol/mol creatinine in a Friday afternoon sample (corresponding to a daily dose of 17 µg) corresponds to a risk of 16.4×10^{-6}.

0.5 µmol/mol creatinine (detection limit of current analytical techniques) corresponds to cancer risk of 1.64×10^{-6}.

While these calculations to estimate daily dose are not precise and include some assumptions, biomonitoring is currently the best method to estimate the total exposure to MOCA in occupational settings. Therefore when biomonitoring data are available, these can be used to estimate cancer risks for occupational exposure.

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