Health Council of the Netherlands

Methyl methacrylate

Health-based recommended occupational exposure limit

Gezondheidsraad
Health Council of the Netherlands

Aan de staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies over *Methyl methacrylate*
Uw kenmerk : DGA/G/TOS/93/07732A
Ons kenmerk : U-6899/JR/bp/459-U66
Bijlagen : 1
Datum : 16 december 2011

Geachte staatssecretaris,

Graag bied ik u hierbij aan het advies over de gevolgen van beroepsmatige blootstelling aan methylmethacrylaat.

Dit advies maakt deel uit van een uitgebreide reeks, waarin gezondheidskundige adieswaarden worden afgeleid voor concentraties van stoffen op de werkplek. Het genoemde advies is opgesteld door de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en omgeving.

Ik heb dit advies vandaag ter kennisname toegezonden aan de staatssecretaris van Infrastructuur en Milieu en aan de minister van Volksgezondheid, Welzijn en Sport.

Met vriendelijke groet,

prof. dr. L.J. Gunning-Schepers,
voorzitter

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Dutch Expert Committee on Occupational Safety
A Committee of the Health Council of the Netherlands

to:

the State Secretary of Social Affairs and Employment

No. 2011/38, The Hague, December 16, 2011

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Preferred citation:
Health Council of the Netherlands. Methyl methacrylate. Health-based recommended occupational exposure limit. The Hague: Health Council of the Netherlands, 2011; publication no. 2011/38.

ISBN: 978-90-5549-880-2

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Samenvatting

Vraagstelling

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid leidt de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) van de Gezondheidsraad, gezondheidskundige advieswaarden af voor stoffen in de lucht waaraan mensen beroepsmatig blootgesteld kunnen worden. Deze aanbevelingen vormen de basis voor wettelijke grenswaarden, vast te stellen door de minister, waarmee de gezondheid van de werknemers beschermd kan worden.

In 1994 heeft de Gezondheidsraad een advies uitgebracht met een evaluatie van de gezondheidsrisico's als gevolg van beroepsmatige blootstelling aan methylmethacrylaat (MMA). Jaren later heeft ook de Europese Scientific Committee on Occupational Exposure Limits (SCOEL) een advies uitgebracht over deze stof. In het voorliggende rapport actualiseert de commissie haar advies uit 1994 door gebruik te maken van het SCOEL advies uit 2005 en latere gepubliceerde gegevens.

De conclusies van de commissie berusten op de wetenschappelijke publicaties die vóór oktober 2011 zijn verschenen.

Fysische en chemische eigenschappen

MMA is een heldere, kleurloze, ontvlambare vloeistof met een scherpe geur. De verbinding kan gemakkelijk polymeriseren onder invloed van licht, hitte, zuurstof, ioniserende straling en katalysatoren.

MMA wordt gebruikt in verven, acrylaatemulsies, polyvinyltoevoegingen, vezels en onverzadigde polyesterharsen, en wordt onder meer toegepast in acrylaatplastic (plexiglas, perspex), kunstnagels, protheses (zoals botcement en kunstgebitten) en als coating van contactlenzen.

Monitoring

Concentraties van MMA in de lucht kunnen worden gemeten en geanalyseerd met behulp van gaschromatografische methoden. Een gevalideerde analysemethode is voorhanden (NIOSH methode 2537).

Huidige grenswaarden

De huidige grenswaarde in Nederland is 205 mg/m^3. In het buitenland lopen de grenswaarden uiteen van 42 mg/m^3 (Finland) tot 410 mg/m^3 (Verenigde Staten). De SCOEL heeft een grens van 205 mg/m^3 voorgesteld. Enkele landen hebben, net als in Nederland, ook een grenswaarde vastgesteld voor korte blootstelling (concentratie gemiddeld over 15 minuten). Voor Nederland is dat 410 mg/m^3. In het buitenland loopt het uiteen van 210 mg/m^3 (Finland) tot 600 mg/m^3 (Zweden). De SCOEL adviseerde een grenswaarde voor korte blootstelling van 410 mg/m^3 te hanteren.

Kinetiek

MMA wordt gemakkelijk opgenomen door de huid en de luchtwegen. Eenmaal opgenomen via de mond of in het bloed door middel van een injectie, verspreidt het zich snel door het lichaam. MMA wordt omgezet door enzymatische hydrolyse. Bij hoge dosering kunnen de hydrolyse-enzymen echter verzadigd raken. In dat geval bindt MMA aan glutathion en worden thioethers gevormd die worden uitgescheiden in de urine. De halfwaardetijd, dat is de tijd die het lichaam nodig heeft om de concentratie MMA in het bloed te halveren, varieert bij de mens tussen de 47 en 55 minuten (bij toediening van lage doses). Bij ratten is vastgesteld dat MMA na biotransformatie voornamelijk uit het lichaam wordt verwijderd

door het uit te ademen als koolzuurgas (binnen twee uur 65% van de toegediende dosis, binnen tien dagen oplopend naar zo'n 88%). Ongeveer de helft van de overgebleven dosis wordt via de urine uitgescheiden, de rest blijft achter in de weefsels. Minder dan één procent van de toegediende dosis wordt uitgeademd als onveranderd MMA.

Effecten

Waarnemingen bij mensen

MMA kan bij de mens irritatie geven aan de huid, ogen en de slijmvliezen van de bovenste luchtwegen. Daarnaast veroorzaakt het specifieke overgevoeligheid en reacties op de huid (dermatitis) bij direct contact, wat wijst op allergie. Er zijn ook enkele gevallen gerapporteerd dat MMA allergische reacties zou veroorzaken na inademing, wat gepaard ging met klachten zoals astma en hoesten. De commissie merkt op dat irritatie en allergie vergelijkbare klachten kunnen opleveren; wellicht dat beide effecten tegelijkertijd optreden. Alleen door het meten van specifieke overgevoeligheid met behulp van immunologische tests kan uitsluitsel worden gegeven of sprake is van allergie. Voor zover bekend zijn die tests niet uitgevoerd voor MMA; in slechts enkele gevallen wordt melding gemaakt van een inhalatieprovocatietest, waarin de patiënten een overgevoeligheidsreactie vertoonde, maar bij deze onderzoeken zijn geen blootstellingsniveaus gemeten. Al met al is er geen duidelijk bewijs dat MMA door inademing tot specifieke overgevoeligheid en bijvoorbeeld allergische astma kan leiden.

Mensen die beroepsmatig blootstonden aan MMA rapporteerden aspecifieke klachten, zoals hoofdpijn, vermoeidheid, concentratieverlies, misselijkheid, versnelde hartwerking, het optreden van een gevoel van koude en doofheid. Zo werd een groep studenten tandheelkunde gedurende vijf uur blootgesteld aan gemiddeld 12 tot 55 mg MMA/m^3. De meest voorkomende klachten na de blootstelling waren hoofdpijn (52%), duizeligheid (51%) en neusirritatie (36%). Ook werden enkele gevallen van moeilijk ademen, hoesten, misselijkheid, concentratieverlies en oogirritatie gerapporteerd. In dit onderzoek ontbrak echter een controlegroep van niet-blootgestelden. In een ander klein onderzoek waarin vloerleggers blootstonden aan zo'n 258 tot 2.500 mg MMA/m^3 (gemeten over een periode van acht uur), werden onder andere een verminderde zenuwgeleiding in armen en benen en slijmvliesirritatie gerapporteerd, maar bleek de longfunctie normaal te zijn. Bij veel onderzoek is onduidelijk bij welke blootstelling en onder welke blootstellingsomstandigheden precies de beschreven effecten optraden, en betrof het geïsoleerde gevallen of deelname van een kleine groep mensen.

Er zijn epidemiologische onderzoeken uitgevoerd waarbij de onderzoekers trachtten een correlatie te vinden tussen blootstellingsniveau en het optreden van klachten in de luchtwegen (onder andere moeilijk ademhalen door neus, chronische hoest) die wijzen op mogelijk neusirritatie. Lichte klachten die daarop wezen werden gerapporteerd bij blootstellingsniveaus van MMA onder de 100 mg/m^3 (gemeten als een achturige gemiddelde concentratie; Pausch e.a. 1994, Marez e.a. 1992/1993, Pickering e.a. 1993). De onderzoeken vertoonden echter beperkingen in opzet en rapportage.

De commissie heeft ten slotte geen aanwijzingen gevonden dat blootstelling aan MMA kanker bij de mens veroorzaakt, of de vruchtbaarheid en het nageslacht aantast.

Waarnemingen bij dieren

MMA is irriterend voor de huid van knaagdieren en de ogen van konijnen. Met behulp van specifieke tests kon verder worden vastgesteld dat cavia's en muizen overgevoeligheidreacties voor MMA vertoonden.

Inademing van MMA veroorzaakte sterfte bij knaagdieren die eenmalig werden blootgesteld aan zeer hoge concentraties (bijvoorbeeld een sterfte van 50 procent onder ratten bij een achturige blootstelling van MMA van 15.000 mg/m^3). Eenmalige blootstelling aan veel lagere concentraties leidde bij ratten tot weefselschade in de neus (810 mg/m^3) en verminderde elektrische activiteit in de hersenen (1.665 mg/m^3). Ratten die voor korte duur herhaalde malen werden blootgesteld aan 475 mg MMA/m^3 vertoonden een verminderde darmpassage vergeleken met niet-blootgestelde ratten. De relevantie voor de mens van deze bevinding is voor de commissie echter onduidelijk. In een ander kortdurend onderzoek met herhaalde blootstelling werden in muizen aanwijzingen voor neusirritatie gevonden bij 4.100 mg MMA/m^3, maar niet bij lagere blootstellingen.

Onafhankelijk van elkaar hebben Lomax e.a. (1997) en het Amerikaanse National Toxicology Program (NTP) gerapporteerd over chronisch inhalatieonderzoek uitgevoerd met ratten, muizen en hamsters, die gedurende een paar maanden tot twee jaar bijna dagelijks werden blootgesteld aan verschillende concentraties MMA (laagste niveau, 104 mg/m^3; hoogste niveau, 4.100 mg/m^3). Het laagste blootstellingsniveau waarbij nog effecten werden waargenomen was 410 mg/m^3. Het betrof irritatie van het reukweefsel in de neus, een lokaal effect.

Wat mogelijke kankerverwekkendheid betreft, werd in het NTP-onderzoek in een groep vrouwelijke ratten bij 2.050 mg/m^3 een verhoogd aantal gevallen van leukemie waargenomen vergeleken met een controlegroep. Andere aanwijzingen dat MMA mogelijk kanker zou kunnen veroorzaken zijn er niet, ook niet in

onderzoek met andere dieren. De onderzoekers van het NTP-onderzoek meldden ook een negatieve trend in de ontwikkeling van tumoren, bijvoorbeeld een afname van longtumoren, tumoren in de hypofyse en levertumoren in mannelijke ratten (2.050 mg/m^3), vergeleken met een groep niet-blootgestelde dieren. Al met al vindt de commissie dat er onvoldoende aanwijzingen zijn voor de mogelijke kankerverwekkendheid van MMA.

Er zijn enkele dierexperimentele onderzoeken gedaan naar de mogelijke effecten van MMA op de ontwikkeling van het nageslacht. Dat heeft wisselende resultaten opgeleverd. In één onderzoek werd bijvoorbeeld vertraagde botvorming gevonden in het nageslacht van vrouwelijke ratten die waren blootgesteld gedurende de zwangerschap aan 520 of 4.480 mg MMA/m^3. In een ander onderzoek werden echter geen effecten op het nageslacht waargenomen (blootstellingen van 1.265 en 4.900 mg/m^3).

Evaluatie en advies

Het meest consistente en beschreven effect na beroepsmatige inademing van lage concentraties MMA is lokale irritatie in de slijmvliezen van de bovenste luchtwegen, met name in de neus. Dierexperimentele onderzoeken bevestigen dat MMA de slijmvliezen kan irriteren. Het gaat vooral om effecten die snel kunnen optreden tijdens of kort na de blootstelling, en die bij langdurige blootstelling (in dieren) tot chronische ontstekingsverschijnselen in luchtwegen kunnen leiden. Ook systemische effecten en aspecifieke symptomen kunnen optreden zoals een depressie van het centrale zenuwstelsel en hoofdpijn.

Voor het afleiden van een gezondheidskundige advieswaarde hebben gegevens afkomstig van epidemiologisch onderzoek de voorkeur boven gegevens van dierexperimenteel onderzoek. De commissie heeft de epidemiologische gegevens geëvalueerd en daarbij een aantal tekortkomingen geconstateerd. Het gaat onder meer om kleine onderzoekspopulaties, het ontbreken van een statistische analyse, onzekerheid over de exacte blootstellingsniveaus en mogelijke hoge piekblootstellingen. Al met al komt de commissie tot de conclusie dat de epidemiologische gegevens onvoldoende zijn om daaruit een gezondheidskundige advieswaarde te kunnen afleiden. Daarom baseert de commissie de advieswaarde op dierexperimentele gegevens.

Lomax en anderen (1997) en de NTP (1986) rapporteerden irritatie van het reukslijmvlies in ratten (en in de NTP-studie ook in muizen), nadat de dieren gedurende twee jaar waren blootgesteld aan MMA (zes uur per dag, vijf dagen per week). Op grond van mechanistische overwegingen beschouwt de commissie de effecten op het reukslijmvlies (olfactoire slijmvliesweefsel) in de neus echter

als niet relevant voor de mens. In de twee dierexperimenten trad ook schade op in het respiratoire slijmvliesweefsel van de neus. De commissie heeft besloten dit laatste type gegevens te gebruiken voor het afleiden van een gezondheidskundige advieswaarde.

De commissie geeft er de voorkeur aan om de gegevens van Lomax en anderen te gebruiken, omdat deze onderzoekers de dieren aan lagere concentraties hebben blootgesteld, in een blootstellingsgebied waarin een duidelijke toename van effecten is waargenomen, in tegenstelling tot de NTP-studie. Met behulp van een benchmarkdosis-analyse heeft de commissie een BMDL* afgeleid van 482 mg/m^3.

Voor het afleiden van een gezondheidskundige advieswaarde heeft de commissie in beschouwing genomen dat irritatie een lokaal effect is. Dit betekent dat de BMDL niet hoeft te worden gecompenseerd voor verschillen tussen dieren en mensen. De commissie past echter wel een onzekerheidsfactor van drie toe in verband met mogelijke verschillen in gevoeligheid tussen mensen. Toepassing van de onzekerheidsfactor levert een gezondheidskundige advieswaarde op voor MMA van afgerond 160 mg/m^3 (482 mg/m^3 gedeeld door drie), gemiddeld over een achturige werkdag.

De commissie leidt uit de beschikbare gegevens af dat piekblootstellingen mogelijk een rol spelen bij snel optredende effecten. Er zijn echter geen goed uitgevoerde epidemiologische of dierexperimentele onderzoeken beschikbaar waar sprake was van alleen piekblootstelling, zodat geen wetenschappelijk onderbouwde gezondheidskundige advieswaarde kan worden afgeleid om te beschermen tegen de mogelijke schadelijke gevolgen van korte blootstellingen.

Gezondheidskundige advieswaarde

De Commissie Gezondheid en beroepsmatige blootstelling aan stoffen stelt een gezondheidskundige advieswaarde voor methylmethacrylaat voor van 160 mg/m^3, gemiddeld over een achturige werkdag.

SCOEL

De commissie heeft geconstateerd dat haar aanbeveling lager is dan die van de Europese SCOEL (160 versus 205 mg/m^3), alhoewel het verschil marginaal is. In

* De BMDL is de onderste concentratie van het 95% betrouwbaarheidsinterval van de benchmarkdosis en vormt het startpunt voor het afleiden van een gezondheidskundige advieswaarde.

beide situaties is de gezondheidskundige advieswaarde voor MMA gebaseerd op dezelfde set aan gegevens. De SCOEL heeft de resultaten over de effecten op het olfactoire slijmvliesweefsel in de neus van knaagdieren en mens als uitgangspunt genomen, terwijl de commissie gekozen heeft voor effecten op het respiratoire slijmvliesweefsel.

Executive summary

Scope

At request of the Minister of Social Affairs and Employment, the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council, proposes health-based recommended occupational exposure limits (HBR-OELs) for chemical substances in the air in the workplace. These recommendations serve as a basis in setting legally binding occupational exposure limits by the Minister.

In 1994, the Health Council published an advice on the toxicity of methyl methacrylate (MMA). In 2005, the Scientific Committee on Occupational Exposure Limits (SCOEL), an advisory committee of the European Committee, published an evaluation on the toxicity of methyl methacrylate as well. In the present advice, the Committee reconsidered the former health-based occupational exposure limit for methyl methacrylate, based on the report of the SCOEL, and additional studies published since 2005. The Committee's conclusions are based on scientific publications which were publised up to October 2011.

Physical and chemical properties

MMA is a clear, colourless, inflammable liquid with a sharp odour. The compound can polymerise readily under the influence of light, heat, oxygen, ionising radiation, and catalysts.

MMA is used in the manufacture of paints, acrylate emulsions, polyvinyl additives, fibres, and unsaturated polyester resins. There are many applications, such as in acrylate plastic (Plexiglass, Perspex), artificial nails, protheses (such as bone cement and dentures), and in coating of contact lenses.

Monitoring

Concentrations of MMA in the air can be measured and analysed by gas chromate-graphic methods. A validated analytical method is available (NIOSH method 2537).

Current limit values

Currently, in the Netherlands a legally binding occupational exposure limit (OEL) of 205 mg/m^3 is set. In other countries OELs vary from 42 mg/m^3 (Finland) to 410 mg/m^3 (the Unites States of America). The European SCOEL adviced an OEL of 205 mg/m^3. In the Netherlands, also an exposure limit of 410 mg/m^3 for short-term exposure (15-minute time weighted average concentration) is set. In other countries, the short-term OEL varies from 210 mg/m^3 (Finland) to 600 mg/m^3 (Sweden). The SCOEL advised a short-term OEL for MMA of 410 mg/m^3.

Kinetics

MMA is easily absorbed through the skin and the respiratory tract. Once taken up orally or by intravenous injection, MMA is distributed quickly throughout the body. The compound is metabolized by enzymatic hydrolysis. At high doses, however, these enzymes can be saturated. In that case, MMA binds to glutathione to form thioethers, which are excreted from the body via the kidneys into the urine. In humans, the half-life of MMA in the circulation varies between 47 and 55 minutes (when low doses are administered). In rats it is observed that MMA after biotransformation is excreted mainly from the body via expiration of carbon dioxide (65% of the administered dose within two hours; 88% within ten days). About half of the remaining dose is excreted via the urine, the rest remains in the tissues of the body. Less than one percent of the administered dose is expired unchanged.

Effects

Observations in humans

In humans, MMA can irritate the skin, the eyes and the mucous membranes of the upper respiratory tract. It also causes specific sensitization and reactions in the skin (dermatitis) on direct contact, suggesting allergic potential. There are cases reported that MMA would cause allergic reactions on inhalation, with symptoms such as asthma and cough. The Committee notes that irritation and allergy can cause comparable symptoms; it is well possible that both types of effects occur simultaneously. Only by performing specific sensitisation measurements using immunological tests, a decisive answer can be given whether or not it concerns allergy. So far, for MMA no such tests have been performed; in a few case-reports inhalation provocation tests have been performed in which patients showed positive specific sensitisation reactions. However, in those cases no data on exposure levels were reported. Overall, there is no clear evidence that inhalation of MMA can cause specific sensitisation and allergic reactions, like asthma, in humans.

Furthermore, workers exposed to MMA reported non-specific symptoms, such as headache, fatigue, loss of concentration, nausea, tachycardia, the sense of cold, and a feeling of deafness. For instance, a group of dental students were exposed to MMA at a concentration of on average 15 to 55 mg/m^3. The main complaints reported were headache (52%), dizziness (51%), and nose irritation (36%). Also some students reported difficulty in breathing, coughing, nausea, loss of concentration, and eye irritation. This study did not include a control group of non-exposed volunteers. In another small investigation, floor layers were exposed to approximately 258 to 2,500 mg MMA/m^3 (measured as an 8-hour TWA). The workers showed decreased velocity conduction in the nerves of the arms and legs, and irritation of the mucous membranes. Lung function was however normal. In most studies, it is unclear at what exposure level and under what exposure conditions, the observed effects occurred. In addition, most studies concerned isolated cases, and participation of a small group of people.

A few epidemiological studies have been performed in which the investigators tried to correlate the level of exposure of MMA to respiratory symptoms (*e.g.*, impaired nose breathing, chronic cough), suggesting that the exposed workers showed nose irritation. Slight symptoms of nose irritation were reported at exposure levels below 100 mg/m^3 (averaged over an 8-hour period;

Pausch et al. 1994, Marez et al. 1992/1993, Pickering et al. 1993). However, all these studies showed limitations in study design and reporting.

Finally, the Committee did not find indications that exposure to MMA causes cancer in humans, or affects the fertility or development of the progeny.

Animal studies

MMA is irritating to the skin of rodents, and to the eyes of rabbits. Using tests for measuring specific sensitisation, MMA caused sensitisation in guinea pigs and mice.

In rats, inhalation of MMA was lethal after a single exposure for eight hours (LD_{50} of 15,000 mg/m^3). A single exposure to much lower concentrations of MMA resulted in tissue damage in the nose (810 mg/m^3), and lowered electrical activity of the brain (1,665 ± 90 mg/m^3). Also in rats, subchronic exposure to MMA at a concentration of 475 mg/m^3 induced decreased intestinal transit performance. However, to the Committee the relevance of this finding for humans is unknown. In another short-term study using mice, signs of nose irritation were observed at 4,100 mg/m^3, but not at lower exposure levels.

Independently from each other, Lomax et al. (1997), and the US National Toxicology Program (NTP, 1986), performed chronic inhalation studies, using rats, mice and hamsters, which were exposed to various levels of MMA (lowest level, 104 mg/m^3; highest level, 4,100 mg/m^3) for a few months up to two-years. The lowest exposure level at which effects were observed was 410 mg/m^3. It concerned irritation of the olfactory epithelium of the nasal cavity, a local effect.

Regarding carcinogenic potential, in the NTP-study, at 2,050 mg MMA/m^3, in a group of female rats an increased incidence in mononuclear cell leukemia was found compared to the control group. There are no other indications that MMA could induce cancer, also not in other animal studies. In contrast, the investigators of the NTP-study reported negative trends in tumour development, such as decreased incidence of lung tumours, liver tumours (male rats only at 2,050 mg/m^3), and tumours in the pituitary gland, compared to the animals in the non-exposed control groups. In conclusion, the Committee is of the opinion that there are insufficient indications for possible carcinogenic properties of MMA.

A few animal studies have been performed on the potency of MMA to affect fertility and development of the progeny, with inconsistent outcomes. For instance, in one study the investigators found delayed ossification in the offspring of female rats, which had been exposed during pregnancy to 520 or 4,480 mg MMA/m^3. In another study, however, no effects on development have been observed (exposure levels of 1,265 and 4,900 mg/m^3).

Evaluation and recommendation

The most consistent and relevant effect described after occupational inhalation of low concentrations of MMA is local irritation to the mucous membranes of the upper respiratory tract, mainly in the nose. Animal experiments confirm that MMA can irritate the mucous membranes. It concerns effects that occur shortly after or during exposure, and which may result in chronic inflammation in the upper respiratory tract after long-term exposure (at least in animals). Also, exposure results in non-specific systemic effects, such as depression of the central nervous system, and headache.

In deriving a health-based recommended occupational exposure limit, data obtained from epidemiological studies are preferred above data from animal experiments. The Committee noted several flaws in the epidemiological data, such as small study population, lack of statistical analysis, and uncertainty about exposure levels, including possible high peak exposures. Therefore, the Committee considers the quality of the epidemiological studies, and the data presented, insufficient to derive a well-founded HBR-OEL, and, therefore, prefers to base it on animal data.

Lomax et al. (1997) and the NTP (1986) reported irritation in the olfactory tissue in the nose of rats (NTP also in mice), after the animals had been exposed for two years (six hours a day, five days a week). However, the Committee considers effects on the olfactory tissue in rats and mice as not relevant for humans, because of mechanistic reasons. In the two studies also adverse health effects in the respiratory epithelium of the nasal cavity have been described. Since no susceptibility differences between rodent and humans are anticipated regarding this type of tissue, the Committee decided to use these data in deriving an HBR-OEL.

The Committee prefers to use the data reported by Lomax et al. (1997), since in that study lower exposure levels were used, in an exposure range where a clear increase in effect size was observed, in contrast to the NTP-study. A benchmark dose analysis revealed a BMDL of 482 mg/m^3. In addition, the Committee considered that irritation is a local effect, indicating no necessity to use an additional uncertainty factor to extrapolate the findings in animal studies to the human situation. However, an uncertainty factor of three is applied to compensate for inter-individual differences among humans. Taking this uncertainty factor into account, the Committee derives an HBR-OEL of 160 mg/m^3 (rounded-off; 482 mg/m^3 divided by three), as an 8-hour time weighted averaged concentration.

The Committee noted that peak exposure might contribute to the occurrence of acute effects. There are, however, no well-performed human or animal studies available with peak exposure only. Therefore, no scientifically well-founded HBR-OEL can be derived to protect against the possible adverse health effects after peak exposure.

Health-based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Safety proposes a health-based recommended occupational exposure limit for methyl methacrylate of 160 mg/m^3, as an eight-hour time weighted averaged concentration.

SCOEL

The Committee noted that its recommendation is lower than the value recommended recently by the SCOEL (160 versus 205 mg/m^3), although the difference can be considered small. Both recommendations are based on the same set of data. The SCOEL based its recommendation on the olfactory epithelial tissue in rodents and humans, whereas the Committee based its recommendation on data on the respitatory epithelial nose tissue.

Part I

Health-based recommended occupational exposure limit for methyl methacrylate

Chapter 1

Scope

1.1 Background

At request of the Minister of Social Affairs and Employment (Annex A), the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council, performs scientific evaluations on the toxicity of chemical substances that are used in the workplace. The purpose of these evaluations is to recommend a health-based occupational exposure limits (HBR-OEL) for concentrations in the air, provided the database allows derivation of such a value. In the Netherlands, these recommendations serve as basis in setting public occupational exposure limits by the Minister.

In this advisory report, such an evaluation is made for methyl methacrylate (MMA). In 1994, the Health Council published already an advice on this compound, and recommended on an HBR-OEL. About ten years later, in 2005, the Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Commission published an advisory report on the toxicity of MMA as well.[12,25] In the present advisory report, DECOS reconsiders the former HBR-OEL, based on data described in the previous report, the document of the SCOEL, and relevant additional human and animal studies, which are not mentioned in the two advisory reports.

1.2 Committee and procedure

The present document contains the re-assessment of MMA by DECOS, hereafter called the Committee. The members of DECOS are listed in annex B.

In 2011, the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in Annex C. The Committee has taken these comments into account in deciding on the final version of the present report.

1.3 Data

The present advisory report is divided in two parts. *Part one* contains the summary evaluation on the toxicity of MMA, and a reconsideration for an HBR-OEL. The evaluation and reconsideration are based on data presented in Part two of the present report.

Part two constitutes the Health Councils' advisory report that was published in 1994, supplemented (in italic) with relevant data obtained from the SCOEL document, and additional publications in the literature (search period up to October 2011; online databases ToxLine, MedLine and Chemical Abstracts (CAPlus)).

Chapter 2

Hazard Assessment

2.1 Hazard identification

In Part 2 of this advisory report, available data on exposure to MMA and adverse health effects in humans and animals are described, which were adopted from the previously published advisory report on the compound by the Health Council (1994), and supplemented with information obtained from the document by the SCOEL (2005), and other published scientific literature.[12,25]

The most consistent and relevant effect described after occupational inhalation of low concentrations of MMA is local irritation to the mucous membranes of the upper respiratory tract, mainly in the nose. Animal experiments confirm that MMA can irritate the mucous membranes. It concerns effects that occur shortly after or during exposure, and which may result in chronic inflammation in the upper respiratory tract after long-term exposure (at least in animals). Also, exposure results in non-specific, systemic effects, such as depression of the central nervous system, nausea, tachycardia, and headache. Exposure levels of MMA at which adverse health effects are observed are shown in Annex D regarding observations in humans, and in Annex E regarding animal studies. The data are sorted by exposure level in ascending order.

Furthermore, dermal contact may lead to irritation of the skin and the eyes. Also various studies indicate that dermal exposure to MMA induces sensitization in humans and animals. No reliable data are available that inhalation of MMA

might induce sensitization and allergic reactions, such as asthma, in the respiratory tract of humans.[4]

The Committee found no indications that exposure to MMA could cause cancer in humans; data from animal experiments showed insufficient evidence that MMA could induce cancer. At the levels tested, reproduction toxicity was not observed.

2.2 Quantitative assessment of the health risk

In deriving an HBR-OEL, data obtained from epidemiological studies are preferred above data from animal experiments. There have been epidemiological studies published by Marez et al. (two separate studies: 1992, 1993), Pausch et al. (1994), and Pickering et al. (1993), all focusing on respiratory effects, including occupational asthma. Marez et al. (1992, 1993) did not find clear exposure-related lung function changes among exposed workers (1992), whereas respiratory symptoms (chronic cough) were minimal; no effects on the heart were observed. The only finding by Pausch et al. (1994) was a clear exposure-related transient eye and nose irritation, which according to the authors correlated with peak exposure. Although Pickering et al. (1993) found a case of possible occupational asthma among workers, specific inhalation challenge and immunological tests to confirm this diagnosis were not performed. Some workers in that study reported irritation to the eyes and respiratory system, but these were according to the authors probably due to high transient exposure. Overall, slight symptoms of nose irritation were reported at exposure levels below 100 mg/m^3. The highest average exposure levels in these studies were reported to be up to 160 mg/m^3 ($\approx$ 40 ppm) (see also Annex D).

The Committee noted several flaws in these studies, which makes it difficult to use these studies in deriving an HBR-OEL. For instance, regarding Marez et al. (1992, 1993), the study populations were small, exposure was monitored stationary, and no statistical analysis was performed. Furthermore, in one of the Marez-studies (1992) data were not adjusted for smoking habits. In the study by Pausch et al. (1994), an in-company study, also no adjustments were made for smoking habits, no statistical analysis was performed, the study population was small, and did not include a non-exposed control group. The study by Pickering et al. (1993) focused mainly on occupational asthma. In all the studies, exposure levels were uncertain, and possibly included high peak exposures. In conclusion, the Committee considered the quality of the epidemiological studies, and the data presented, insufficient to derive a well-founded HBR-OEL, and, therefore, preferred to base it on animal data.

Lomax et al. (1997), and the National Toxicology Program (NTP, 1986; Chan et al. 1988), performed long-term animal studies. In these studies, groups of rats (and also mice in the NTP-study) inhaled MMA at different concentrations (Lomax-study, 0, 25, 100, and 400 ppm; NTP, 0, 250 (females only), 500, and 1,000 (males only) ppm), for six hours a day, five days a week, for a period of two years.

The Committee noted that in both studies, and in both animal species, MMA induced damage in the olfactory epithelium in the nasal cavity. This was explained by the presence of high levels of the enzyme carboxyl esterase in the olfactory epithelium of rats (and mice).[SCOEL4, SCOEL5, SCOEL6, SCOEL7] The enzyme metabolizes MMA to methacrylic acid, which is considered the toxic end product of MMA.[3]

In human olfactory tissue the levels of carbocylesterases are significantly less, and this is also the case for the respiratory epithelium in the nasal cavity of rodents.[2,18,20] This difference in carboxyl esterase levels is the most likely explanation for the higher susceptibility for MMA-induced damage in the olfactory tissue in rodents than humans. In addition, humans have a different structure of the upper respiratory tract compared to rats and mice. [1,11,14] Rats and mice have a highly developed olfactory system with a complex nasal turbinate structure, which increases airflow turbulence. Approximately 50% of the total surface area of the rat nasal cavity is lined with olfactory epithelium. Humans, in contrast, have relatively poorly developed turbinate structures, and much less developed olfactory systems that cover only about 10% of the nasal cavity.[1,11,14] Overall, the Committee considers the tissue damage of the olfactory epithelium observed in rodents of insufficient relevance for humans, because of anatomical and MMA specific susceptibility differences between rodents and humans.

Lomax et al. and the NTP reported also on other effects, such as irritation of the respiratory epithelium of the nasal cavitiy. Since no MMA-related susceptibility differences between rodents and humans have been described for this type of tissue, the Committee considers these effects relevant for humans, and based its recommendation on this effect. In addition, the Committee prefers to use the data reported by Lomax et al. (1997), since that study applied lower exposure levels in an exposure range where a clear increase in effect size was observed, in contrast to the NTP-study. The findings by Lomax et al. are shown in Table 2.1. The irritant effects are similar as those observed by the NTP, and both studies complement each other well (Figure 2.1).

Table 2.1 Histopathologic findings in the nose tissue of rats, which were exposed to MMA for 6 hours/day, five days/week for two years (Lomax et al. 1997).[17]

	Exposure level			
	0 mg/m^3 (0 ppm)	104 mg/m^3 (25 ppm)	416 mg/m^3 (100 ppm)	1,664 mg/m^3 (400 ppm)
Male rats, olfactory epithelium: number of animals	39	47	48	38
- Degeneration/atrophy. Dorsal meatus	0	0	42	38
- Basal cell hyperplasia	5	3	33	33
- Replacement by ciliated epithelium	0	0	1	15
- Inflammation chronic/acute, mucosa/submucosa	0	0	17	29
Male rats, respiratory epithelium: number of animals	44	47	48	42
- Inflammation chronic/acute, mucosa/submucosa	4	0	2	26
- Hyperplasia, submucosal gland/goblet cell	1	0	1	25
- Hyperplasia, focal, ciliated epithelium	0	0	0	2
- Adenoma, polypoid	0	0	1	1
Female rats, olfactory epithelium: number of animals	44	45	41	41
- Degeneration/atrophy. Dorsal meatus	0	0	24	39
- Basal cell hyperplasia	0	1	18	31
- Replacement by ciliated epithelium	0	0	7	21
- Inflammation chronic/acute, mucosa/submucosa	0	0	5	25
Female rats, respiratory epithelium: number of animals	45	45	41	42
- Inflammation chronic/acute, mucosa/submucosa	2	0	0	9
- Hyperplasia, submucosal gland/goblet cell	0	0	1	9
- Hyperplasia, focal, ciliated epithelium	0	0	0	0
- Adenoma, polypoid	0	0	0	0

Using the benchmark dose software of the US Environmental Protection Agency, a BMDL of 482 mg/m^3 was calculated, which corresponds to an extra risk of ten percent, compared to background risk levels (see Annex F).

The calculated BMDL serves as point of departure in deriving an HBR-OEL. The Committee considered that irritation is a local effect, indicating no necessity to use an additional uncertainty factor to extrapolate the findings in animal studies to the human situation. However, an uncertainty factor of three is applied to compensate for inter-individual differences among humans. Taking this uncertainty factor into account, the Committee derives an HBR-OEL of 160 mg MMA/m^3 (rounded-off; 482 mg/m^3 divided by three), as an 8-hour time weighted averaged concentration.

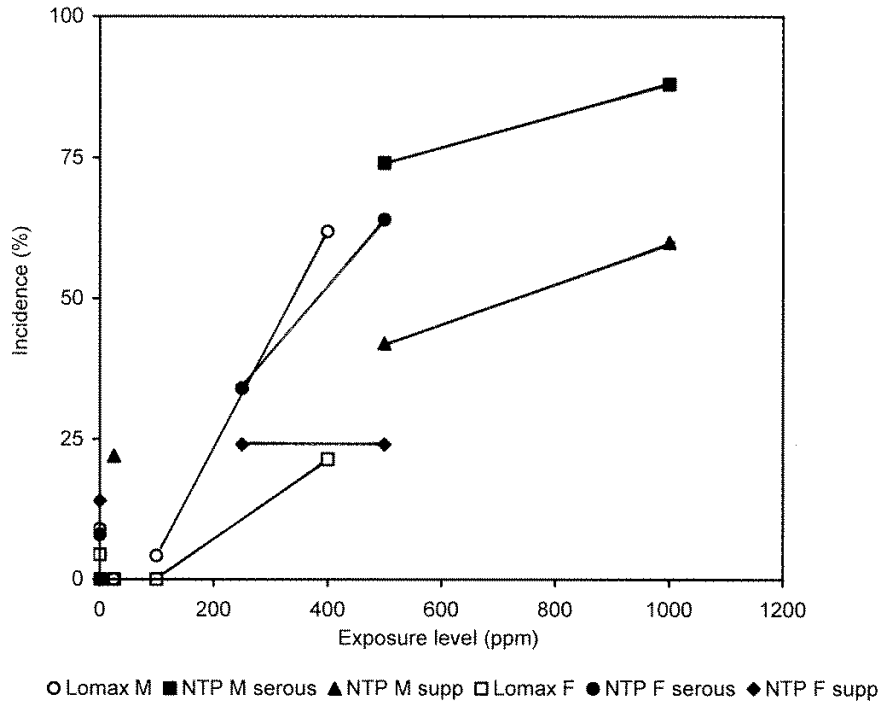


Figure2.1 Shown are data on the incidence of inflammation in the respiratory epithelium of the nose of male and female rats. Abbreviations used: F, female; M, male; serous, serous inflammation; supp, suppurative inflammation. Open circles and squares represent data by Lomax et al. Source: Lomax et al. (1997) and the NTP (1986).[17, NTP88]

The Committee noted that peak exposure might contribute to the occurrence of acute effects. There are, however, no well-performed human or animal studies available with peak exposure only. Therefore, no scientifically well-founded HBR-OEL can be derived to protect against the possible adverse health effects after peak exposure.

2.3 Skin notation

The absorption rate through human skin in vitro was 152 µg MMA/cm^2/h in the occluded situation, and 3.48 µg MMA/cm^2/h in the unoccluded situation (Ward and Heylings 1993). A skin notation is considered appropriate when the absorption rate is more than 0.25 x HBR-OEL =40 mg/cm^2 (ECETOC 1993). Therefore, a skin notation is not considered necessary.

2.4 Groups at extra risk

Because of the irritating properties of MMA, workers with hyperreactive airways are at extra risk. Those who are already sensitized to acrylates are at extra risk at skin contact.

2.5 Health-based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Safety proposes a health-based recommended occupational exposure limit for methyl methacrylate of 160 mg/m^3, as an eight-hour time weighted averaged concentration.

2.6 SCOEL

The Committee noted that its recommendation is lower than the recommendation by the SCOEL, although the difference can be considered small (160 versus 205 mg/m^3). Both recommendations are based on the same set of data. The SCOEL based its recommendation on the olfactory epithelial tissue in rodents and humans, whereas the Committee based its recommendation on data on the respitatory epithelial nose tissue.

Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request

for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a ‘exposure versus tumour incidence range’ and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in Annex B.

Annex **B**

The Committee

- G.J. Mulder, *chairman*
  Emeritus Professor of Toxicology, Leiden University, Leiden,
- R.B. Beems
  Toxicologic Pathologist, formerly employed at the National Institute for Public Health and the Environment, Bilthoven
- P.J. Boogaard
  Toxicologist, Shell International BV, The Hague
- J.J.A.M. Brokamp
  Social and Economic Council, The Hague, *advisor*
- D.J.J. Heederik
  Professor of Risk Assessment in Occupational Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht
- R. Houba
  Occupational Hygienist, The Netherlands Expertise Centre for Occupational Respiratory Disorders, Utrecht
- H. van Loveren
  Professor of Immunotoxicology, Maastricht University, Maastricht, and National Institute for Public Health and the Environment, Bilthoven
- T.M. Pal
  Occupational Physician, Netherlands Center for Occupational Diseases, Amsterdam

- A.H. Piersma
  Professor of Reproductive Toxicology, Utrecht University, Utrecht, and National Institute for Public Health and the Environment, Bilthoven
- H.P.J. te Riele, Professor of Molecular Biology, VU University Amsterdam, Amsterdam
- I.M.C.M. Rietjens
  Professor of Toxicology, Wageningen University and Research Centre, Wageningen
- G.M.H. Swaen*
  Epidemiologist, Dow Benelux N.V., Terneuzen
- R.C.H. Vermeulen
  Epidemiologist/Environmental Hygienist, Institute for Risk Assessment Sciences, Utrecht University, Utrecht
- R.A. Woutersen
  Professor of Translational Toxicology, Wageningen University, Wageningen, and TNO Quality of Life, Zeist
- P.B. Wulp
  Occupational Physician, Labour Inspectorate, Groningen
- J.M. Rijnkels, *secretary*
  The Health Council, The Hague

Part II of this advice is based on the 1994 report of the Health Council and the 2008 report of the Scientific Committee on Occupational Exposure Limits (SCOEL), and was updated in 2009 by P.J.M. Weterings, Weterings Consultancy BV, Rosmalen, the Netherlands.

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairman and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the

* Due to conflict of interest, G Swaen is acting as an external advisor, and not as a member.

Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

Comments on the public review draft

A draft of this advisory report was released in 2011 for public review. The following organisations and persons have commented on the draft:

- T.J. Lentz, National Institute of Occupational Safety and Health, USA
- P.J. De Vries, Technocentrum Vloeren, The Netherlands
- H. Müllerschön, CEFIC Methacrylate Sector Group, Belgium.

Annex **D**

Observation in humans

Data on inhalation exposure only.

Exposure level of MMA	Effects	Type of study and subjects in study	Occupational setting end/or study design	Reference
Mean, 0.5-4 mg/m^3; range 0-48 mg/m^3	No statistically significant excess in all-cause or cause-specific mortality found.	Mortality study; 1,561 workers exposed to MMA; 237 death certificates evaluated (123 from non-exposed, and 114 from exposed workers).	Source of information were death certificates.	Collins et al. 1989
2 – 200 mg/m^3	Number of workers with complaints: headache, 119; pain in the extremities, 45; excessive fatigue, 32; sleep disturbance, 32; loss of memory, 30; irritability, 32.	Case-control study; 152 workers exposed for years (no further details given).	No details available.	IARC 1979, DFG 1984
Average, 12-55 mg/m^3; range, 6.7-68.2 mg/m^3	Headache (53%); dizziness (51%); sinus irritation (36%); and few cases of irritation to skin, loss of concentration, breathing difficulty, hunger, nausea, coughing, irritation to the eyes, and tachycardia.	Case-control study; 147 dental students constructing acrylic trays containing MMA.	Environmental monitoring for 5 hours. No further details available. *Remark:* Study did not include a non-exposed control group.	Pagniano et al. 1986 (also as quoted in ECETOC 1995)[6]

Area 1, 120-160 mg/m^3 (30-40 ppm); *Area 2*, 80-120 mg/m^3 (20-30 ppm); *Area 3*, 40-80 mg/m^3 (10-20 ppm); *Area 4*, 12-40 mg/m^3 (3-10 ppm).	Mild to moderate symptoms included impaired nose breathing (6/211); dry nose (6/211); rhinitis (1/211); reduced sense of smell (2/211); eye irritation and lacrimation (3/211), chronic bronchitis (2/211). The only finding that showed clear evidence of a MMA-induced effect was transient eye and nose irritation, which correlated with peak exposure.	Medical survey; 211 exposed male workers at a polyMMA sheet production factory; *area 1*, N=56; *area 2*, N=20; *area 3*, N=128; *area 4*, N=7. Most workers were doing shift work.	Personal air sampling as 8-h average values. Average expressed as geometric means. Incidence of high peak concentration reported between 410 mg/m^3 (100 ppm) up to 1,230 mg/m^3 (300 ppm). Method included questionnaire and visual examination of nasal cavity. *Remarks:* This study is an in-company study of unknown quality. It did not include a non-exposed control group. Data were not adjusted for smoking habits and no statistical analysis was performed.	Pausch et al. 1994
Factory one: mean, 74 mg/m^3 (18.5 ppm); range 36-128 mg/m^3 (9-32 ppm). *Factory two*: Average, 86 mg/m^3 (21.6 ppm); range, 48-160 mg/m^3 (11.9-38.5 ppm).	No signs of cardiomyodystrophy; more supraventricular and ventricular ectopic beats measured among exposed subjects (p<0.01); depolarisation changes observed only among exposed subjects.	Medical survey among workers (N=22) manufacturing polyMMA on effects of MMA on the heart. Study included 18 healthy controls.	Atmospheric levels of MMA was monitored for 8 hours; also 1-hour peak exposure levels measured. Test included continuous ambulatory electrocardiographic records. *Remarks*: Authors did not discuss possibility that observed effects were related to peak exposure. No correction was made for smoking habits.	Marez et al. 1992
Factory one: mean, 74 mg/m^3 (18.5 ppm); range 36-128 mg/m^3 (9-32 ppm). *Factory two*: Average, 86 mg/m^3 (21.6 ppm); range, 48-160 mg/m^3 (11.9-38.5 ppm).	Chronic cough was the only increased chest symptom reported among exposed workers (p=0.04). Spirometry revealed only an increased MEF_{50} and MEF_{50}/MEF (p=0.04). FEV_1 and FEV_1/FVC values were normal. Results remained unaffected after adjustment for smoking habits.	Medical survey among workers (N=40) manufacturing polyMMA on effects of MMA on the heart. Study included 45 healthy controls.	Atmospheric levels of MMA was monitored for 8 hours; also 1-hour peak exposure levels measured. Test included questionnaire and spirometry. *Remarks*: No personal monitoring data presented. Authors did not discuss possibility that observed effects were related to peak exposure. The Committee considers changes in MEF_{50} only not indicative for airway obstruction.	Marez et al. 1993

Distribution in groups: low (<4 g/m^3, <1 ppm), medium (20 mg/m^3; 5 ppm), and high (80 mg/m^3; 20 ppm). Most likely transient peaks of up to 2,000 mg/m^3 (500 ppm) occurred.	1) *Cross-sectional study.* One case suggestive of occupational asthma, but tests to confirm this were not performed. Some workers reported on irritation to the eyes and respiratory system, particularly following high, transient exposure. 2) *Follow-up study.* No clear evidence for respiratory sensitisation found.	1) *Cross-sectional study.* Workers (N=384) of a manufactory of polyMMA acrylic sheet and liquid MMA composites. 2) *Follow-up study.* Workers of the same manufactory who were not available in the first study, a population of past leavers (N=83), and workers identified as having two or more work-related respiratory symptoms in the cross-sectional study.	In the cross-sectional study, exposure in the past years was as high as 410 mg/m^3 (100 ppm). Health tests consisted of lung function testing and health questionnaire.	Pickering et al. 1993[6,25]
258-2,500 mg/m^3 (as 8 h TWA)	Complaints reported were: irritation of the mucous membranes, effects on CNS, neurasthemia, general somatic complaints; some nerves showed lowered conduction velocity; lung function was normal.	Case-control study; ten floor-layers; non-exposed control group included (unknown source).	Personal air sampling; exposure was measured in large and small rooms under several ventilations conditions; lung function testing was performed by the subjects themselves.	Lindberg et al. 1991
Up to 1,560 mg/m^3	Asthmatic reactions.	Case-report; one operating room nurse.	Peak exposure levels, measured during handling.	Pickering et al. 1986

Annex **E**

Animal studies

Summary of animal data on repeated inhalation.

Exposure level of MMA	Effects	Animal species	Study design	References
104 mg/m^3 (25 ppm)	No exposure-related effects have been observed.	Male and female Fischer rats (N=70/sex/group), and Syrian Golden hamsters (N=56/sex/ group); study included non-exposed control groups.	Exposure was for 6 hours/day, 5 days/ week for 24 months (rats) and 18 months (hamsters). Gross and histopathologic examinations performed at termination of exposure period (in rats also after 3 and 12 months in study). Nasal tissues of rats were re-examined by Lomax (microscopic examination from at least 10% of randomly selected rats from each group).	Lomax et al. 1997(based on data by Röhm and Haas 1979)[6,17,29]
256 mg/m^3 (63 ppm)	None of the rats and mice died before the end of the study. No compound-related effects observed in any of the animals.	F344 rats, and B6C3F1 mice; 5 animals per species/sex/ group; included non-exposed groups as control.	Ten-day study: exposure was for 6 hours/day, for 9 days over a 10-day period. Animals killed at day 11 after start of exposure.	NTP 1986, Chan et al. 1988

256 mg/m^3 (63 ppm)	No compound-related deaths and pathologic effects observed in any of the animals.	F344 rats, and B6C3F1 mice; 10 animals per species/sex/ group; included non-exposed groups as control.	Fourteen-week study: a) rats at ITB, 6 hrs/d, 5 d/wk for 65 exposure over 97 d; b) mice at ITB, 6 hrs/d, 5 d/ wk for 64 exposure over 96 d; animals killed at the end of the exposure period.	NTP 1986, Chan et al. 1988
406 mg/m^3 (99 ppm)	Study concerned effects on development. Food consumption of pregnant rats was decreased. No compound-related effects on development in litters were observed.	Pregnant (Crl:CD) rats, N=23/group, including controls (N=25).	Exposure was for 6 hours/day, on gestation days 6 through 15.	Solomon et al. 1991, 1993
410 mg/m^3 (100 ppm)	*Rats*. Exposure-related and concentration-dependent microscopic changes in the olfactory epithelium lining the dorsal maetus in the anterior region of the nasal cavity (including, degeneration/atrophy, hyperplasia of basal cells, replacement of olfactory epithelium by ciliated epithelium). The squamous epithelium of the nasal cavity was not affected. *Hamsters*. No compound-related effects have been observed in any of the animals.	Male and female Fischer rats (N=70/sex/group), and Syrian Golden hamsters (N=56/sex/ group); study included non-exposed control groups.	Exposure was for 6 hours/day, 5 days/week for 24 months (rats) and 18 months (hamsters). Gross and histopathologic examinations performed at termination of exposure period (in rats also after 3 and 12 months in study). Nasal tissues of rats were re-examined by Lomax (microscopic examination from at least 10% of randomly selected rats from each group).	Lomax et al. 1997(based on data by Röhm and Haas 1979)[6,17,29]
410 mg/m^3 (100 ppm)	No compound-related effects (differences in blood pressure, ECG, heart and respiratory rates) have been observed in any of the animals.	Female beagle dogs (N= 6); study included non-exposed control groups.	Exposure was for 6 hours/day, 5 days/week for 3 months. Gross and histopathologic examinations performed at termination of exposure period.	Smith et al. 1979, Drees et al. 1979 (abstract only)[5]
475 mg/m^3 (116 ppm)	*After 3 months*: Effect observed was marked lowered subcutaneous adiposity. *After 6 months*: Effects observed included lowered subcutaneous adiposity, significant decreased intestinal transit performance (p<0.05).	Male Sprague Dawley rats (N = 25/time point). One group served as non-exposed control (N=25/ time point).	Exposure was for 8 hours/day, 5 days/ week for 3 or 6 months.	Tansy et al. 1980a/b
512 mg/m^3 (125 ppm)	None of the rats and mice died before the end of the study. No compound-related effects observed in any of the animals.	F344 rats, and B6C3F1 mice; 5 animals per species/sex/ group; included non-exposed groups as control.	Ten-day study: exposure was for 6 hours/day, for 9 days over a 10-day period. Animals killed at day 11 after start of exposure.	NTP 1986, Chan et al. 1988
512 mg/m^3 (125 ppm)	No compound-related deaths and pathologic effects observed in any of the animals.	F344 rats, and B6C3F1 mice; 10 animals per species/sex/ group; included non-exposed groups as control.	Fourteen-week study: a) rats at ITB, 6 hrs/d, 5 d/wk for 65 exposure over 97 d; b) mice at ITB, 6 hrs/d, 5 d/ wk for 64 exposure over 96 d; animals killed at the end of the exposure period.	NTP 1986, Chan et al. 1988

512 mg/m^3 (125 ppm)	Study concerned effects on development. No maternal toxicity was observed. In offspring delayed ossification was observed. No further data available.	Pregnant rats.	Exposure was for two hours, once every three days on gestation days 8 through 18.	Luo et al. 1986
1,025 mg/m^3 (250 ppm)	None of the rats and mice died before the end of the study. No compound-related effects observed in any of the animals.	F344 rats, and B6C3F1 mice; 5 animals per species/sex/ group; included non-exposed groups as control.	Ten-day study: exposure was for 6 hours/day, for 9 days over a 10-day period. Animals killed at day 11 after start of exposure.	NTP 1986, Chan et al. 1988
1,025 mg/m^3 (250 ppm)	No compound-related deaths and pathologic effects observed in any of the animals.	F344 rats, and B6C3F1 mice; 10 animals per species/sex/ group; included non-exposed groups as control.	Fourteen-week study: a) rats at ITB, 6 hrs/d, 5 d/wk for 65 exposure over 97 d; b) mice at ITB, 6 hrs/d, 5 d/ wk for 64 exposure over 96 d; animals killed at the end of the exposure period.	NTP 1986, Chan et al. 1988
1,025 mg/m^3 (250 ppm)	No significant differences in survival compared to controls observed. In the nasal epithelium, serous and suppurative inflammation, and degeneration of the olfactory epithelium was observed at increased incidence compared to controls.	Female F344 rats; 50 animals per group; included non-exposed groups as control.	Two-year study: Exposure was for 6 hrs/d, 5 d/ week for 102 weeks; animals were killed at the end of the exposure period.	NTP 1986, Chan et al. 1988
1,246 mg/m^3 (304 ppm)	Study concerned effects on development. Food consumption of pregnant rats was decreased. No compound-related effects on development in litters were observed.	Pregnant (Crl:CD) rats, N=22/group, including controls (N=25).	Exposure was for 6 hours/day, on gestation days 6 through 15.	Solomon et al. 1993
1,640 mg/m^3 (400 ppm)	*Rats*. Exposure-related and concentration-dependent microscopic changes in the olfactory epithelium lining the dorsal maetus in the anterior region of the nasal cavity (including, degeneration/atrophy, hyperplasia of basal cells, replacements of olfactory epithelium by ciliated epithelium). The squamous epithelium of the nasal cavity was not affected. Also changes in the respiratory epithelium (hyperplasia) were observed in the anterior region of the nasal cavity. *Hamsters*: Decreased body weights and increased mortality was observed. No other compound-related effects have been observed in any of the animals.	Male and female Fischer rats, and Syrian Golden hamsters; study included non-exposed control groups.	Exposure was for 6 hours/day, 5 days/week for 24 months (rats), and 18 months (hamsters). Gross and histopathologic examinations performed at termination of exposure period (in rats also after 3 and 12 months in study).	Lomax et al. 1997(based on data by Röhm and Haas 1979)[6,17,29]
1,640 mg/m^3 (400 ppm)	No compound-related effects (differences in blood pressure, ECG, heart and respiratory rates) have been observed in any of the animals.	Female beagle dogs (N= 6); study included non-exposed control groups.	Exposure was for 6 hours/day, 5 days/week for 3 months. Gross and histopathologic examinations performed at termination of exposure period.	Smith et al. 1979, Drees et al. 1979 (abstracts only)[5]

2,050 mg/m^3 (500 ppm)	None of the rats and mice died before the end of the study. No compound-related effects observed in any of the animals.	F344 rats, and B6C3F1 mice; 5 animals per species/sex/ group; included non-exposed groups as control.	Ten-day study: exposure was for 6 hours/day, for 9 days over a 10-day period. Animals killed at day 11 after start of exposure.	NTP 1986, Chan et al. 1988
2,050 mg/m^3 (500 ppm)	None of the rats died before the end of the study. No compound-related effects observed in any of the animals (rats and mice).	F344 rats, and B6C3F1 mice; 5 animals per species/sex/ group; included non-exposed groups as control.	Eleven day-study. Exposure was for 6 hours/day for a total of ten exposure over 11 days. Animals killed at the end of the exposure period.	NTP 1986, Chan et al. 1988
2,050 mg/m^3 (500 ppm)	*Rats and mice at ITB*: no compound-related deaths and pathologic effects observed in any of the animals. *Rats and mice at BNW*: All animals survived the exposure period.	F344 rats, and B6C3F1 mice; 10 animals per species/sex/ group; included non-exposed groups as control.	Fourteen-week study: a) rats at ITB, 6 hrs/d, 5 d/wk for 65 exposure over 97 d; b) mice at ITB, 6 hrs/d, 5 d/wk for 64 exposure over 96 d; c) rats at BNW, 6 hrs/d, 5 d/wk over 14 wk, 65 exposures; d) mice at BNW, 6 hrs/d, 5 d/wk over 14 wk, 64 exposures; animals killed at the end of the exposure period.	NTP 1986, Chan et al. 1988
2,050 mg/m^3 (500 ppm)	*Rats*: No significant difference in survival of exposed animals observed compared to controls. Effects observed included: mononuclear cell leukaemia (20/50, females, compared to 11/50 in controls), inflammation of the nasal cavity (serous inflammation: 37/50, males, 32/50 females; suppurative inflammation: 21/50 males, 12/50, females), degeneration of the olfactory sensory epithelium (39/50, males, 44/50, females), increase in alveolar macrophages in the lungs (20/49, males, 14/50 females). *Mice*: No significant difference in survival compared to controls observed. Effects included: inflammation of the nasal cavity (37/50, males; 42/49 females), epithelial hyperplasia in the nasal cavity (44/50, males; 43/49, females), cytoplasmic inclusion of nasal mucosa (46/50, males; 44/49, females), degeneration of the olfactory sensory epithelium (48/50, meals; 44/49, females). Also negative trends in certain tumours were observed: lung tumours (adenomas: 1/50, males; 10/50 control males), pituitary gland tumours (adenomas: 3/44 females, 12/49 control females), hepatocellular adenomas and	F344 rats, and B6C3F1 mice; 50 animals per species/sex/ group; included non-exposed groups as control.	Two-year study: Exposure was for 6 hrs/d, 5 d/ week for 102 weeks; animals were killed at the end of the exposure period.	NTP 1986, Chan et al. 1988

	carcinomas (3/48, males; 9/50 control males; 4/48, females; 7/50, control females).			
4,100 mg/m^3 (1,000 ppm)	None of the rats and mice died before the end of the study. No compound-related effects observed in any of the animals.	F344 rats, and B6C3F1 mice; 5 animals per species/sex/ group; included non-exposed groups as control.	Ten-day study: exposure was for 6 hours/day, for 9 days over a 10-day period. Animals killed at day 11 after start of exposure.	NTP 1986, Chan et al. 1988
4,100 mg/m^3 (1,000 ppm)	None of the rats died before the end of the study. No compound-related effects observed in any of the animals. In mice, compound-related effects included dyspnoea and redness and swelling of the nasal region.	F344 rats, and B6C3F1 mice; 5 animals per species/sex/ group; included non-exposed groups as control.	Eleven day-study. Exposure was for 6 hours/day for a total of ten exposure over 11 days. Animals killed at the end of the exposure period.	NTP 1986, Chan et al. 1988
4,100 mg/m^3 (1,000 ppm)	*Rats and mice at ITB*: no compound-related deaths and pathologic effects observed in any of the animals. *Rats and mice at BNW*: all animals survived the exposure period.	F344 rats, and B6C3F1 mice; 10 animals per species/sex/ group; included non-exposed groups as control.	Fourteen-week study: a) rats at ITB, 6 hrs/d, 5 d/wk for 65 exposure over 97 d; b) mice at ITB, 6 hrs/d, 5 d/ wk for 64 exposure over 96 d; c) rats at BNW, 6 hrs/d, 5 d/ wk over 14 wk, 65 exposures; d) mice at BNW, 6 hrs/d, 5 d/ wk over 14 wk, 64 exposures; animals killed at the end of the exposure period.	NTP 1986, Chan et al. 1988
4,100 mg/m^3 (1,000 ppm)	*Rats*: No significant difference in survival of exposed animals observed compared to controls. Effects observed included: inflammation of the nasal cavity (serous inflammation: 44/50); suppurative inflammation: 30/50), degeneration of the olfactory sensory epithelium (42/50), increase in alveolar macrophages in the lungs (16/49). Negative trends observed for pituitary and preputial gland tumours. *Mice*: No significant difference in survival compared to controls observed. Other effects observed were: minimal to mild (7/10, males), and mild to moderate (10/10, females) inflammation of the nasal turbinates.	Male F344 rats, and male and female B6C3F1 mice; 50 animals per species/sex/ group; included non-exposed groups as control.	Two-year study: Exposure was for 6 hrs/d, 5 d/ week for 102 weeks; animals were killed at the end of the exposure period.	NTP 1986, Chan et al. 1988
4,100 mg/m^3 (1,000 ppm)	Microscopic indications of damage to the tracheal mucosa observed. No other histopathological findings observed.	Male Sprague Dawley rats (N = 10). One group served as non-exposed control (N=9).	Exposure was for 56 hours over a 7-day period	Tansy et al. 1980c
4,480 mg/m^3 (1,080 ppm)	Study concerned effects on development. No maternal toxicity was observed. In offspring delayed ossification, and an increase in number of resorptions were observed. No further data available.	Pregnant rats.	Exposure was for two hours, once every three days on gestation days 8 through 18.	Luo et al. 1986

4,900 mg/m^3 (1,178 ppm)	Study concerned effects on development. Food consumption of pregnant rats was decreased. A significant but transient decreases in maternal body weight gain was observed on gestation days 8, 10 and 13. No compound-related effects on development in litters were observed.	Pregnant (Crl:CD) rats, N=23/group, including controls (N=25).	Exposure was for 6 hours/day, on gestation days 6 through 15.	Solomon et al. 1993
8,200 mg/m^3 (2,000 ppm)	Final mean body weights of rats were 10 to 19% lower than those of controls. In mice, compound-related effects included dyspnoea and redness and swelling of the nasal region.	F344 rats, and B6C3F1 mice; 5 animals per species/sex/ group; included non-exposed groups as control.	Eleven day-study. Exposure was for 6 hours/day for a total of ten exposure over 11 days. Animals killed at the end of the exposure period.	NTP 1986, Chan et al. 1988
8,200 mg/m^3 (2,000 ppm)	*Rats*: One male and three females rats died before the end of the exposure period. Malacia and gliosis in the brain were observed in 5/9 females. *Mice*: Two males died before the end of exposure. Effects observed included: the kidneys pathologies (1/10, males), inflammation nasal turbinates (4/10, males; 5/10, females), metaplasia nasal epithelium (10/10, males; 10/10, females).	F344 rats, and B6C3F1 mice; 10 animals per species/sex/ group; included non-exposed groups as control.	Fourteen-week study: c) rats at BNW, 6 hrs/d, 5 d/ wk over 14 wk, 65 exposures; d) mice at BNW, 6 hrs/d, 5 d/ wk over 14 wk, 64 exposures; animals killed at the end of the exposure period.	NTP 1986, Chan et al. 1988
8,437 mg/m^3 (2,028 ppm)	Study concerned effects on development. Food consumption of pregnant rats was decreased. A significant but transient decreases in maternal body weight gain was observed on gestation days 8, 10, 13 and 16. No compound-related effects on development in litters were observed.	Pregnant (Ctr: CD^{r}BR) rats, N=22-25/group.	Exposure was for 6 hours/day, on gestation days 6 through 15.	Solomon et al. 1993
12,300 mg/m^3 (3,000 ppm)	Final mean body weights of rats were 10 to 19% lower than those of controls. Two of the five female rats died before the end of study. In mice, compound-related effects included dyspnea and redness and swelling of the nasal region.	F344 rats, and B6C3F1 mice; 5 animals per species/sex/ group; included non-exposed groups as control.	Eleven day-study. Exposure was for 6 hours/day for a total of ten exposure over 11 days. Animals killed at the end of the exposure period.	NTP 1986, Chan et al. 1988
12,300 mg/m^3 (3,000 ppm)	*Rats*: One and nine females died before the end of the exposure period. Male and females showed lower final body weights compared to controls. In surviving females malacia and gliosis was found in the brain.	F344 rats, and B6C3F1 mice; 10 animals per species/sex/ group; included non-exposed groups as control.	Fourteen-week study: c) rats at BNW, 6 hrs/d, 5 d/ wk over 14 wk, 65 exposures; d) mice at BNW, 6 hrs/d, 5 d/ wk over 14 wk, 64 exposures; animals killed at the end of the exposure period.	NTP 1986, Chan et al. 1988
20,500 mg/m^3 (5,000 ppm)	All rats and mice died before the end of study.	F344 rats, and B6C3F1 mice; 5 animals per species/sex/ group; included non-exposed groups as control.	Eleven day-study.Exposure was for 6 hours/day for a total of ten exposure over 11 days. Animals killed at the end of the exposure period.	NTP 1986, Chan et al. 1988

20,500 mg/m^3 (5,000 ppm)	*Rats*: All exposed animals died before the end of the exposure period. Effects observed included bone marrow atrophy (8/10, males), extensive cerebellar peduncles (early-death females), malacia and gliosis of the brain (females, dying late in the study). Mice: Eight males and eight females died before the end of the exposure period. Effects observed included: Effects observed included: the kidneys pathologies (5/10, males), inflammation nasal turbinates (8/10, males; 8/10, females), metaplasia nasal epithelium (10/10, males; 10/10, females), extensive necrosis in the liver (3/10, males).	F344 rats, and B6C3F1 mice; 10 animals per species/sex/ group; included non-exposed groups as control.	Fourteen-week study: c) rats at BNW, 6 hrs/d, 5 d/ wk over 14 wk, 65 exposures; d) mice at BNW, 6 hrs/d, 5 d/ wk over 14 wk, 64 exposures; animals killed at the end of the exposure period.	NTP 1986, Chan et al. 1988
39,300 or 65,500 mg/m^3 (9,430 and 15,700 ppm)	Liver and kidney degeneration.	Dogs.	Exposure was for 0.5 hour/ day for 15 days, or for 1.5 hours/day for 8 days.	Spealman et al. 1945
39,300 or 65,500 mg/m^3 (9,430 and 15,700 ppm)	Liver degeneration (swollen cells with altered nuclei).	Guinea pigs.	Exposure was for 3 hours/day for 3 days.	Spealman et al. 1945
111,000 mg/ m^3 (27,000 ppm)	Study concerned effects on development. Initial decrease in maternal food consumption and body weight observed. In the offspring decreased foetal body weight and foetal crown-rump length, and delayed ossification of the vertebrae were observed.	Pregnant Sprague Dawley rats, N=22-27/group.	Exposure was for approximately 17 or 54 minutes per day, on gestation days 6 through 15.	Nicholas et al. 1979

Summary of animal data on single inhalation (excluding mortality data).

Exposure level of MMA	Effects	Animal species	Study design	References
810 mg/m^3 (200 ppm)	Nasal lesions observed (degeneration or atrophy in the olfactory region of the epithelium).	Rats.	Single exposure for six hours.	Mainwaring et al. 2001
1,664 ± 90 mg/m^3 (400 ppm)	Depression of electrical activity in several areas of the brain.	Rats.	Single exposure for one hour.	Innes and Tansy 1981

Annex **F**

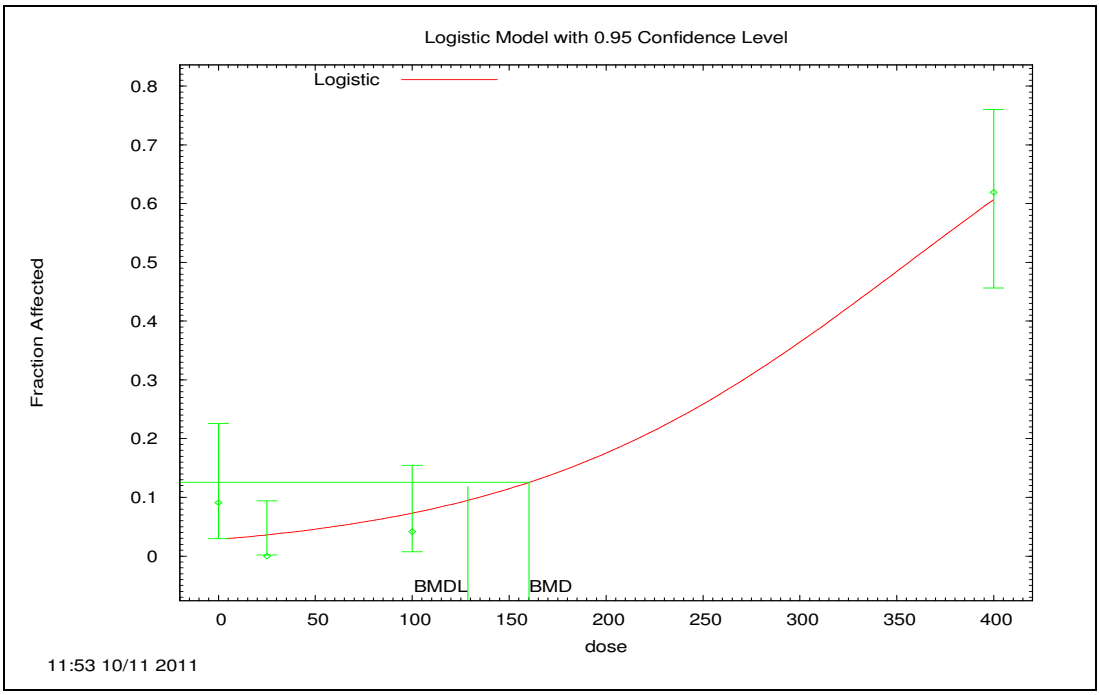
Results of the benchmark dose analysis

Software	: US EPA BMDS version 2.2.
Model type	: Dichotomous, restricted models.
BMR, risk type	: 10%, extra risk.
BMDL	: Lowest 95% confidence interval of the BMD.
Model fitting	: Based on visual inspection of graphs, judgement on BMD-BMDL deviation (model accepted at a deviation of < factor 10), and calculated differences in Log-likelihoods.
Data source	: Lomax et al. (1997). Effect data analysed only when statistical difference between exposed and control group was $p<0.05$.
Exposure	: 6 hours/day, 5 days/week for 24 months; inhalation of MMA.
Effects	: Pathological lesions in the nasal cavity of male and female rats.

Histopathological effects in the nasal cavity		*0 ppm*	*25 ppm*	*100 ppm*	*400 ppm*
Inflammation chronic/acute, mucosa/submucosa	Male	4/44	0/47	2/48	26/42
	Female	2/45	0/45	0/41	9/42
Hyperplasia, submucosal gland/goblet cell	Male	1/44	0/47	1/48	25/42
	Female	0/45	0/45	1/41	9/42

	Lowest BMDL (ppm)	*Lowest BMDL (mg/m³)*[a]	*Model of choice*
Male rats (*inflammation and hyperplasia) See graph*	116	482	LogLogistic
Female rats (*hyperplasia)*	154	641	LogLogistic

[a] 1 ppm = 4.16 mg/m³.



Part II

Summary of data on methyl methacrylate

Chapter 1

Identity, physical and chemical properties, monitoring*

1.1 Identity

Chemical Name	:	Methyl methacrylate
Chemical substance prime name	:	2-propenoic acid, 2-methyl, methylester
CAS registry number	:	80-62-6
Synonyms	:	methyl methacrylate; acrylic acid; 2-methyl-, methylester; methyl-alpha-methylacrylate; methyl-2-methyl-2-propenoate; 2 methyl-2 propenoic acid; methylester; 'monocite' methacrylate monomer

Methyl methacrylate (MMA) is a clear, colourless, flammable liquid with an unpleasant strong acrid odour. (Scolnick and Collins 1986; NTP 1986; Clayton and CIayton 1981)

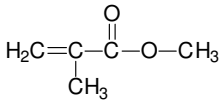
1.2 Physical and chemical properties

The chemical properties are defined by the compound's very reactive double bond. The monomer is readily polymerised by light, heat, oxygen, ionising radiation and catalysts (NTP 1986) because of its ability to form a radical or anion. Polymerisation is an exothermic reaction and can be accelerated by the use of initiators, such as hydrochloric acid. In order to prevent polymerisation, a

* Text cited from the advisory report by the Health Council published in 1994 (1994/09). Additional data from the SCOEL advisory report, and other published data are presented in italic.

small amount of hydroquinone or its monomethylether is added. Polymethyl methacrylate (polyMMA) is toxicologically inert (Clayton and Clayton 1981).

Addition to the double bond of for instance water, alcohol, acids, ammonium, amine, H_2S, and mercaptans, takes place to form isobutyric acid-esters (Wenzel and Lehmann 1978). MMA is soluble in methyl ethyl ketone, tetrahydrofuran, and aromatic and chlorinated hydrocarbons (Windholz 1976).

Chemical Name	:	Methyl methacrylate
CAS registry number	:	80-62-6
Synonyms	:	2-propenoic acid, 2-methyl, methylester; methyl methacrylate acrylic acid; 2-methyl-, methylester; methyl-alpha-methylacrylate; methyl-2-methyl-2-propenoate; 2 methyl-2 propenoic acid; methylester; 'monocite' methacrylate monomer
Molecular formula	:	$C_5H_8O_2$
Structure	:	
Molecular weight	:	100.12
Boiling point (100 kPa)	:	100-10°C
Melting point	:	- 48°C
Vapour pressure	:	3.87 kPa (20°C)
Relative density of the saturated vapour in air	:	1.09 (20°C, 100 kPa, air = 1)
Vapour percentage in saturated air	:	3.8 % (20°C, 100 kPa)
Density of the liquid	:	0.9440 (25°C) (water = 4°C)
Flash point (tag open cup)	:	13°C (Kirk-Othmer 1981); 10°C (Clayton and Clayton 1981)
Explosion limits in air	:	2.1%-12.5 % (20°C, 101 kPa)
Solubility	:	slightly soluble in water, 1.5 g/100 mL; very soluble in alcohol and ether
Log $P_{octanol/water}$	:	1.38 (Tanii and Hashimoto 1982); 0.945 (Dillingham et al. 1983); 0.7 (Fujisawa and Masuhara 1981)
Odour threshold	:	Detection between 0.2 and 0.62 mg/m^3; recognition between 0.85 and 1.9 mg/m^3. (van Gernert and Nettenbrijer 1977; van Gernert 1984)
Conversion factors (20 °C, 100 kPa)	:	1 ppm = 4.16 mg/m^3 1 mg/m^3 = 0.24 ppm

1.3 Analytical methods

1.3.1 Environmental monitoring

NIOSH (1980) analytical method

A known volume of air is drawn through a tube containing XAD-2 resin. MMA is desorbed with carbon disulfide (CS_2). An aliquot of the sample solution is injected into a gas chromatograph (GC) equipped with a flame ionisation detector (FID). This method was validated over the range of 193-725 mg/m^3 and an atmospheric pressure of 762 mm Hg using a 3-liter sample volume. This method was to be revised by June, 1986 (NIOSH 1984). In view of the recommended HBR-OEL value a lower detection limit must be strived for. Alternative GC-FID methods for the determination of MMA in working atmosphere are presented by Kollár et al. (1988) and Morgan and Bradley (1989). Both types are packed with activated carbon GA-I. As extractive agent CS_2 with 5 vol% isopropyl alcohol is used. MMA is determined with GC.FID. The limit of detection under the recommended conditions is 0.8 mg/m^3.

Methacrylates have also been analysed by thin-layer chromatography (TLC), polarography, and colorimetry (Kirk-Othmer 1981). MMA can also be analysed by high performance liquid chromatography (HPLC) and gel-permeation chromatography (GPC) (Kirk-Othmer 1981). Methods have been developed for determination of methacrylates in mixtures with other monomers, in solvents including water, in biological fluids, and in polymers.

1.3.2 Biological monitoring

There is no validated method to analyse MMA in biological material.

Baker et al. (1988) developed a GLC assay for the estimation of MMA in whole saliva, with a lower limit of detection of 1 µg/m^3.

Pfäffli and Svartling (1985) developed a headspace capillary GLC method to analyse MMA in blood. The limit of detection is 0.02 µg/m^3.

Chapter 2

Sources of exposure*

2.1 Natural occurrence

MMA is not known to occur as a natural product. (IARC 1979) However, in a more recent study MMA was found in the extract of the plant *Chishima-sasa* in a concentration of 0.44 g/g. Extracts of the related plant *Karamatsu* did not contain MMA (Yasuhara and Sugiura 1987).

2.2 Man-made sources

2.2.1 Production

The most common way to synthesise MMA is by conversion of acetone cyanohydrin with concentrated sulfuric acid (H_2SO_4), methanol and water. Acetone cyanohydrin is mixed with H_2SO_4 (mol ratio 1:1.5) in a cooling reactor by intensive stirring at 80-100°C. Then the reaction product is heated to 130-150°C and the resultant methacrylamide sulphate is mixed with methanol and water at 90°C to form the crude product, which is contaminated with volatile organic compounds. The product is purified by distillation (Wenzel and Lehmann 1978; IARC 1979) giving a commercial product that is at least 99.6%

* Text cited from the advisory report by the Health Council published in 1994 (1994/09). Additional data from the SCOEL document and other published data are presented in italic.

pure (99.8% in the united State according to NTP (1986) and 99.95% according to Wenzel and Lehmann 1978)) The impurities are: methacrylic acid, 0.003% max; water 0.05% max. It may also contain a small amount of hydroquinone, and its monomethylether as inhibitors. (IARC 1979)

The monomer MMA can be recaptured from the polymer through thermal depolymerisation (cracking) at 350-400°C (Wenzel and Lehmann 1978).

In 1975, three companies in the United States produced 248 million kg; Japanese companies produced 114 million kg MMA. Western European countries produced 220 million kg in 1976 (IARC 1979).

The production came to ca. 750 x103 kg in the Western world in 1977 at a production capacity of 1100 million kg per year (Wenzel and Lehmann 1978). In 1976 the Netherlands imported 0.57 million kg MMA from the United States (IARC 1979).

2.2.2 *Uses*

MMA is primarily used in the manufacturing of polyMMA to fabricate crystal-clear or coloured plastics, the so-called acrylic glasses (Plexiglass, lucite, perspex and altuglass), clear ceramic-like resins, and for acrylic moulding and extrusion powder (Clayton and Clayton 1981; Chan et al. 1988). Western European use of MMA in 1976 was in the production of polyMMA (80%), paints (9.5%), acrylic emulsions (3%) polyvinyl modifiers (3%), fibres (2%) and unsaturated polyester resins (0.5%) (IARC 1979). In the US, approximately 20% of the compound is used to produce copolymers that act as coating binders in acrylic surface coatings, such as latex paint and lacquer (Chan et al. 1988).

The monomer is also used in the manufacture of emulsion polymers such as floor polishes, textile backing coatings, paper coating, sealants and adhesive cements (IARC 1979).

The monomer and polymers have wide applicability in medical technology. MMA serves as a medical spray adhesive or non-irritant bandage solvent. It is also used to coat corneal contact lenses (Clayton and Clayton 1981) and to manufacture artificial nails (Condé-Salazar et al. 1986). In orthopaedic surgery, it is used as bone cement for fixation of metal and plastic prostheses (Scolnick and Collins 1986) and to fill space in bones (NTP 1986). MMA is also used in neurosurgery and surgery of the jaw (Borchard 1981).

To prepare prostheses and orthopaedic devices, a mixture of MMA with prepolymerised oligomers is used, that has to be finished with the preparer's bare hands to obtain the desired dimensions before the final hardening. This is also the case in dentistry where MMA-based material is specifically employed in

removable dentures, orthodontic appliances, occlusal bite plates and splints, veneer crowns, tooth-coloured fillings, and the pit and fissure sealants (Seppäläinen et al. 1984).

Dental and orthopaedic uses of MMA differ from industrial applications. Generally, the latter do not require manual handling of monomer-containing products (Rajaniemi and Tola 1985).

Chapter 3

Environmental levels and human exposure*

3.1 Environmental levels

3.1.1 Water

MMA has been detected the US in drinking water with minimum concentrations of less then 1.0 g/l (USEPA 1975). In New Orleans MMA was identified in commercial deionised charcoal filtered water (Dowty et al. 1975). It could have originated from the plastics used somewhere in the preparation or storage of the ion exchange resins or charcoal (IARC 1979).

MMA has also been detected in plant sewers, waste water (NTP 1986) and river water the US in (IARC 1979).

3.1.2 Food

Residual MMA has been detected in commercial polystyrene plastics at a concentration of 36 mg/kg (IARC 1979), but no information is available about the migration of MMA from plastics to food.

* Text cited from the advisory report by the Health Council published in 1994 (1994/09). Additional data from the SCOEL document and other published data are presented in italic.

3.1.3 *Ambient air (IARC 1979)*

Total emission of MMA to the ambient air in the US in 1974 was estimated by the US Environmental Protection Agency to be 3.6 million kilograms. The sources and amounts were: MMA production, 1.7 million kg; end-product manufacture, 1.7 million kg; bulk storage 0.2 million kg.

In one study in Europe, during the drying of paints based on acrylic resins, emissions of MMA were estimated to range from 139 to 563 gram per hour. In air exhaust stacks of paint plants the concentrations of MMA were estimated to range from 20 to 81 mg/m^3. This is only a fraction of what has been found during the drying of paints.

MMA has been detected as a gaseous product of the combustion of polyMMA.

3.2 Human exposure

3.2.1 *General population*

MMA has been found in the tissues of patients receiving 'bone cement' in dental or orthopaedic surgery; concentrations as high as 7-51 g/kg have been found in the fatty components of bone marrow (no further details; cited by Chan et al. 1988). MMA may be set free from dental fillings even up to 6 days after polymerisation (Borchard 1981).

3.2.2 *Working population*

Groups exposed to MMA are (Delbressine et al. 1981):

- workers in the plastic industry
- laboratory technicians and health profession personnel, who are concerned with the manufacture of prostheses, contact lenses and cosmetic products
- those applying coatings for cellulose and textile fibres, glass and rubber.

In 1974, the US National Institute for Occupational Safety and Health (NIOSH) estimated that 30,000 workers in the US were exposed to MMA (IARC 1979). However, in 1983 a NIOSH national occupational exposure survey estimated that 128,962 workers were exposed to MMA, of which 58,565 were female (RTECS 1990).

In a study of exposure at five plants manufacturing polyMMA sheets, the mean eight-hour TWA exposure ranged from 16-300 mg/m^3, and the TWA highest exposure for workers examined medically was 100-200 mg/m^3 (IARC 1979). In another study in four factories processing polyMMA the concentration of MMA in the air ranged from 0.06 to 4.6 mg/m^3 (Vainiotalo and Pfäffli 1989). The mean concentration in the air of MMA in two factories manufacturing acrylic polymers was 77 and 90 mg/m^3 respectively with a range from 37 to 160 mg/m^3. The recording period was 8 h (Marez et al. 1992). In these two factories, 1-hour peak concentrations between 474 and 1664 mg/m^3 were determined (Marez et al. 1991).

Preparation of impression trays, occlusal splints and orthodontic appliances, moulding and repair of prostheses expose dental technicians, dentists and auxiliary personnel possibly to a higher extent to MMA, because they have to handle it with their bare hands (Rajaniemi 1986).

Darre et al. (1987a) evaluated the air concentrations of MMA emitted from seven commercially available bone cements, during mixing and setting. Measuring time equalled mixing time and was 40-60 sec. The air concentrations (mean of three experiments) ranged from 1770 to 2940 mg/m^3 for the various brands. When stirred for 4 min the MMA concentration was 3450 mg/m^3.

The concentration of MMA in the air of an operating room was measured at four time intervals during three total hip-replacement procedures by McLaughlin et al. (1978), Acrylic cement Simplex P was used which contained MMA, (97.4%), N,N-dimethyl-p-toluidine, (2.6%), and hydroquinone (75 ± 15 ppm). The results were:

- when mixing of the cement started: 832-1170 mg/m^3
- two minutes after mixing started: 230-420 mg/m^3
- six minutes after mixing started: less than 42 mg/m^3
- when the cement hardened in the patient: less than 42 mg/m^3.

Manicurists exposure to MMA during preparation of artificial fingernails has been measured by Froines and Garabrant (1986) in eight nail shops, each of which employed 2 to 17 manicurists. Results are given in Table 1.

The mean intermittent exposure to MMA ranged from 38 to 198 mg/m^3, with an average of 84 mg/rn^3. Peak exposures, the highest single maximum level observed during a procedure, ranged from 64 to 570 mg/m^3 with an average of 223 mg/m^3. The 8-hour TWA-exposure to MMA ranged from 8.7 to 28 mg/m^3, with an average of 22 mg/m^3.

Lindberg et al. (1991) found that during the laying of floors made of polyMMA, exposure to the monomer varied from 258 to 2500 mg/m^3 (62 to 601 ppm) 8 h TWA. Measurements were performed with ten floor-layers equipped with personal air

Table 1 Exposure of manicurists to MMA during preparation of synthetic nails (Fro86).

nail shop	number of measurement (intermittent)	mean intermittent exposure (mg/m^3)[a]	number of measurements (continuous)	mean continuous exposure (mg/m^3)[b]
1	2	148 ± 41[c]	2	23 ± 11
2	2	82 ± 20	5	8.7 ± 2.9
3	6	129 ± 29	7	19 ± 5
4	2	198 ± 147	5	20 ± 5
5	4	65 ± 20	4	19 ± 5
6	2	38 ± 20	7	10 ± 3
7	5	94 ± 60	23	28 ± 3
8	2	74 ± 6	6	25 ± 8
overall	25	84 ± 16	59	22 ± 2

[a] intermittent exposure corresponds to exposure to MMA during the actual period of use of MMA
[b] continuous exposure is the 8-hour TWA
[c] mean exposure ± SE
samplers during the hours that exposure was to be expected, in large and small rooms and under several ventilation conditions. The time between the exposure hours was estimated and in this way the TWA 8 h was calculated. The median value of the exposure time was 20 min and the interval between exposures was approximately 30 - 60 min. No specifications are given as to exposure concentrations in relation to the size of the room or the ventilation conditions

Additional information*

Liljelind et al. (2005 and 2009) measured exposure levels of MMA on the hands of dental technicians, and simultaneously also in the air in the breathing zone of each participant (N=4).[15,16] The overall air levels varied from 5 to 78 mg/m^3, and depended on work tasks.

Exposure to MMA was measured in five dental clinical facilities in Sweden. Whole-day and task-specific short-term measurements were performed. The median eight hour time-weighted averages for MMA were 0.8 µg/m^3 (dentists), and 0.3 µg/m^3 (dental nurses). The maximum short-term exposure level was 151 µg/m^3 for both dentists and dental nurses.[10]

* Data retrieved up to October 2011 and not mentioned in any of the two advisory reports.

Exposure to MMA in the chemical industry (three unidentified methacrylate producing companies) was examined during the period 1998-2000. Both full-shift (≥ six-hour) and short-term (1-30 minutes) measurements were taken. Data were stratified by job classification (monomer production, monomer use, maintenance, distribution, and laboratory operations), and facility. The total number of samples analysed was 376 (334 full-shift, and 42 short-term). Monomer use for manufacturing other products was associated with the highest exposure. Maximum mean values for this job classification per facility were 12.7 ± 13.4, and 17.7 ± 6.1 ppm (52.8 ± 55.7, and 73.6 ± 25.4 mg/m^3) for full-shift and short-term samples, respectively. The highest concentrations determined in individual samples were 65.9 and 26.6 ppm (274.1 and 110.6 mg/m^3), respectively. Incidentally, relevant exposure to MMA occurred in distribution (full-shift average in one plant 8.7 ppm (36.2 mg/m^3), maximum 50.1 ppm (208 mg/m^3)), and maintenance (short-term average in one plant 17.3 ppm (72 mg/m^3), maximum 26.6 ppm (110.7 mg/m^3)).[10,28]

Chapter 4

Toxicokinetics*

4.1 Absorption

Oral, dermal and inhalation studies are available which indicate absorption of MMA in animals (Bratt and Hathway 1977, Verkkala et al. 1983 and Raje et al. 1985). Also for humans Crout et al. (1982) used oral administration. The results from these experiments demonstrate absorption can occur in animals (oral, inhalation and dermal routes) and humans (oral – no other routes measured). Dermal absorption has been studied in vitro through human skin (Ward and Heylings 1993). In healthy humans with acrylic dentures MMA was detected in saliva but not in blood or urine (Baker et al. 1988).

Rajaniemi et al. (1989): After human dermal absorption urinary MMA excretion ranged from 19 to 200 nmol MMA/24 h (1.9-20 µg/24 hr). Without exposure these dental technicians excreted either 6-30 nmol MMA/mmol creatinine or N.D. (less than 0.5 nmol/l). Persons who were never exposed to MMA excreted less than 15 nmol MMA/mmol creatinine. Only a limited number of volunteers (n = 11) was studied and no quantitative data on exposure were available. Therefore, it cannot be confirmed that dermal exposure is occurring. Urine samples were collected after what was considered a normal working day:

* Text cited from the advisory report by the Health Council published in 1994 (1994/09). Conclusions made in 1994 not necessarily mean that these are adopted presently by the DECOS. Additional data from the SCOEL document and other published data are presented in italic.

the estimated time that there was manual contact with the liquid monomer varied from 30 minutes to four hours. As a control a preshift sample was taken and urine was also taken from 10 unexposed persons. The manual contacts were probably scattered over the working period, as there was no consistent pattern in the highest urinary methacrylate concentration in relation to the time of the day. The highest concentration ranged from 16 to 373 nmol MMA/mmol creatinine. It is concluded that the large variation probably reflects differences in exposure rather than differences in metabolism. Four volunteers had dermatitis, but the urinary MMA correlated poorly with it. Five volunteers used protective gels or creams, but Rajaniemi et al. state that this provided only partial protection. Because no exposure data are available the only quantitative conclusion that can be drawn from the study by Rajaniemi et al. (1989) is that MMA excretion after human dermal exposure is two to seven times higher than before exposure.

Ward and Heylings (1993) studied the absorption of MMA in vitro through human abdominal skin. The amount applied was 10 µg/cm^2 under occluded and unoccluded conditions. During the first hour the maximum rate of absorption was 274 µg.cm^{-2}.h^{-1} in the occluded situation and 107 µg.cm^{-2}.h^{-1} in the unoccluded situation. The percentage of the applied dose absorbed through the epidermis during the first hour of exposure was 2.41% for occluded skin and 0.48% for unoccluded skin. After this initial period of maximum absorption, rates reduced to give average overall 0-10 h absorption rates of 152 µg.cm^{-2}.h^{-1} (occluded) and 3.48 µg.cm^{-2}.h^{-1} (unoccluded). The percentage of the applied dose absorbed through the epidermis during the first 10 h of exposure was 15 for occluded skin and 0.56 for unoccluded skin.

Baker et al. (1988) detected MMA in saliva of healthy humans wearing autopolymerised dental appliances. A maximum value of 180 µg/ml was obtained for saliva collected from the fitting surface of the appliance, compared with 40 µg/ml in whole saliva. MMA was not found in any of the blood or urine samples. Three hours after insertion of the acrylic denture the monomer level had fallen to the lower limit for detection in saliva (1 µg/ml). The mechanisms responsible for the fall in the concentration of MMA in saliva, a temperature-dependent process, have not been identified. Hydrolysis to methacrylic acid might be important: the half-life of MMA in human saliva at 37°C is 1.2 hr, in water at 30°C a half-life of more than 3.5 h has been measured. The failure to detect monomer in venous blood and urine can also be ascribed to hydrolysis of MMA.

Verkkala et al. (1983) measured the dermal absorption in a quantitative way. Five male Wistar rats had 12 cm^2 of their tails exposed for 3 h to liquid MMA (occlusive method, evaporation was negligible). After the exposure the amount

absorbed was assayed by weighing the cotton wool pad before and after the test and amounted to 0.78 ± 0.20 g. Although the method is rather crude and can lead to gross overestimation, this study gives at least an indication of the quantity of MMA absorbed. Moreover, the rat tail is hyperkeratinised and is not structurally similar to human skin. The absorption was 22 $mg.cm^{-2}.h^{-1}$.

Additional data in SCOEL document

Experimental animal studies have shown that MMA is rapidly and almost completely (~97%) absorbed into the bloodstream following oral administration (Bratt and Hathway 1977; Bereznowsky 1995[SCOEL1]). A study with rats has shown that 10-20% of inhaled MMA vapour is deposited in the upper respiratory tract; available study results would suggest that following inhalation, much of the dose of MMA passes quickly into the epithelial lining along the length of the respiratory tract (Morris 1992[SCOEL2]; Raje et al. 1985[SCOEL3]).

4.2 Distribution

Dermal studies indicate that MMA is distributed rapidly throughout the body and quantitatively excreted within 24 hr. There are two studies which explicitly deal with distribution kinetics.

The first study (from 1973, described by Borchard 1981, the original publication was not available) showed that 5 min after iv injection of radioactive MMA in Wistar rats the highest activity was found in blood and kidneys. Low concentrations were found in liver and red bone marrow. After 2 h the total activity had decreased and a shift from the bone marrow to the compact bone could be observed. In the period from 4 to 8 hr, activity was found only in skeletal bones, liver, intestine and salivary glands. After 24 hr, total injected MMA was eliminated. No further quantitative data are available.

The second study is by Raje et al. (1985). Groups of four or five male S/D rats were exposed by inhalation to MMA concentration of 416 mg/m^3 (100 ppm) for either 1, 2, 3 or 4 h periods. Following exposure, the animals were removed, and immediately sacrificed by decapitation. The concentration of MMA was determined in blood, brain and lungs. The concentrations are presented in Table 2; they did not change significantly with different exposure periods. Blood shows the highest concentration among the three tissues, while brain concentrates more MMA than the lungs, probably due to its lipid content.

However, it should be noted that the biotransformation studies referred to in the next section also indicate that MMA is rapidly distributed throughout the body, both after intravenous injection and oral administration.

4.3 Biotransformation

MMA is readily biotransformed in each species studied so far. The biotransformation of MMA has been studied in detail. The most frequently reported study is the one by Bratt and Hathway (1977), who demonstrated in rats that MMA is metabolised through the same pathway as the naturally occurring amino acid valine, both after intravenous injection and oral administration. The process is visualised in Figure 1.

Table 2 MMA concentrations[a] in tissues of rats following inhalation exposure (Raje et al. 1985).

exposure time (hr)	blood (mg%)	brain (µg/g)	lungs (µg/g)
1	10.15 ± 1.23	24.36 ± 5.05	23.24 ± 2.03
2	14.28 ± 2.80	30.42 ± 5.60	18.63 ± 1.29
3	9.78 ± 1.90	25.67 ± 6.46	19.98 ± 1.93
4	10.34 ± 1.23	20.52 ± 4.59	20.58 ± 2.40

[a] mean ± SEM (n = 5) for all groups except brain concentrations for 2 hour period (n = 4)

The first step is hydrolysis of MMA (compound 1 in the figure) by carboxylesterase into methacrylic acid (compound 2) and methanol. Both methacrylic acid and valine (compound 3) are metabolised into methylacrylyl-CoA (compound 4), which can be further degraded and taken up in the citric acid cycle.

The main data originate from the above mentioned study in rats, which expired up to 88% of a single dose of ^{14}C-MMA as $^{14}CO_2$ in 10 days, both after intravenous injection and oral administration (Bratt and Hathway 1977). About half the remainder of the dose was excreted in the urine and the rest was retained by the body tissues. Pulmonary excretion of unchanged MMA accounted for less than 1.0% of the dose. These results are confirmed by the study by Crout et al. (1982) who injected two rats ip with radiolabeled MMA.

Bratt and Hathway (1977) also found several of the intermediates of the degradation pathway in the urine, excreted by exposed rats, among them ^{14}C-methacrylic acid (0.8% of the dose), ^{14}C-methyl-malonic acid (1.4% of the dose), ^{14}C-succinic acid (0.2% of the dose) and ^{14}C-HCO^{3-} (up to 7% of the dose). Crout et al. (1982) found a comparable percentage as radioactivity in the urine: 14.5 and 7% (data of two rats).

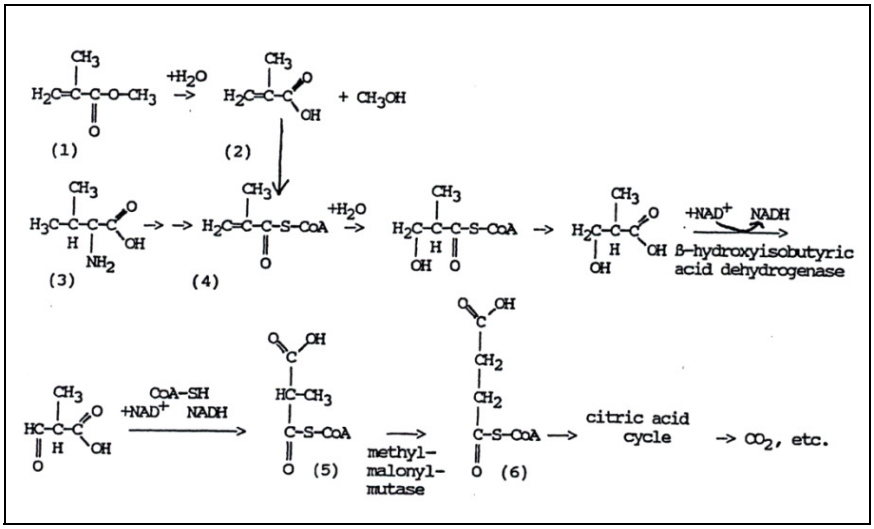


Figure 1 Scheme for the degradation of MMA in mammals (Bratt and Hathway 1977, Crout et al. 1982). Compound 1: MMA; compound 2: methacrylic acid: compound 3: valine: compound 4: methylacrylyl-CoA; compound 5: methylmalonyl-CoA; compound 6: succinyl-CoA.

These data in experimental animals are confirmed by studies in humans. The formation of methacrylic acid from MMA was detected in vitro (Corkill et al. 1976) and in vivo (Crout et al. 1979 and Svartling et al. 1986).

In vitro the half life time of MMA was 20-40 min, as was measured in serum obtained from ten volunteers (Corkill et al. 1976). The data were obtained at low concentrations: 0.1 mM/dm^3. In vivo the half life time of MMA was 47-55 min, as was measured in serum of nine patients who underwent total knee arthroplasty (Svartling et al. 1986). In vitro the half-life time of MMA was 1.2 hr, as was measured in human saliva of six different donors at 37°C. The concentration fell to 10% of its original level after 19 h at 37°C (Baker et al. 1988). In this case the initial concentration was 100 µg/ml.

MMA does not change the hepatic cytochrome P-450 level quantitatively; however, it may induce some qualitative changes. This was found after ip injection in mice (Nilsen et al. 1978) and rats (Elovaara et al. 1983).

When high dosages of MMA are administered, the enzymatic route of hydrolysis of MMA is saturated and detoxification occurs via glutathione conjugation. Thioether excretion increases. Also when carboxylesterases are blocked the thioether excretion increases. Thioether excretion after massive dosing was studied by Elovaara et al. (1983). Thioether excretion after blocking

the carboxylesterase pathway was studied by Delbressine et al. (1981) and depletion of GSH and GSSH after massive dosing was studied by Boyland and Chasseaud (1970) and Elovaara et al. (1983). Further, the excretion of intermediate products was assessed in a vitamin B_{12}-deficient individual (Crout et al. 1982).

A single ip MMA-dose of 2 $g.kg^{-1}$ in rats increased the thioether excretion up to 11 times that of control. Urine collected from 12 to 24 h after the injection still contained 8 times more thioethers than control. In the same experiment three ip injections (one per day) of 1 g/kg in the rat did not increase thioether excretion (Elovaara et al. 1983).

Blocking the carboxylesterase pathway with tri-o-tolyl phosphate (TOTP) increases the thioether excretion even when low dosages of MMA are administered. Delbressine et al. (1981) injected rats ip once with a MMA-dose of 0.14 mmol (14 mg/kg) without and with previous administration of TOTP (0.34 mmol/kg). The thioether excretion increased with 16 µmol per 24 hr, corresponding to with 11% of the dose. Concurrent with this excretion, depletion of hepatic GSH levels was found. Two studies in rats are available. Boyland and Chasseaud (1970) found a hepatic GSH level of 92% of that of the control 30 min after ip injection of 0.87 ml/kg (821 mg/kg). After 2 h the GSH level was 68% of that of the control. The second study used a higher dosage, which induced as a consequence a larger depletion: a single ip dose of 2 g/kg in rats decreased the hepatic GSH level to 20% of that of the control after 3 hr. The GSSH level was decreased to 50% of the control. Depletion in the kidney was less dramatic: after 3 h the renal GSH level was 48% of the control while the GSSH level did not change (Elovaara et al. 1983).

When other steps in the degradation pathway of MMA are blocked, intermediate products can be found in the urine. For instance, patients with vitamin B_{12} deficiency (the conversion of methyl-malonyl-CoA (compound 5 in figure) into succinyl-CoA (compound 6) is blocked) will excrete large amounts of methylmalonic acid. This was found in one vitamin B_{12}-deficient individual, who received as a treatment 1 mg of vitamin B_{12} monthly. An oral dose of 94 mg [Me-$^2H_3$]-MMA resulted in the next 24 h in 1029 µg [Me-$^2H_3$]-methylmalonic acid, detected in the urine, representing approximately 1% of the administered dose (Crout et al. 1982).

Additional data in SCOEL document

According to the SCOEL, in rodents, the nasal epithelium (particularly the olfactory region) is a primary site of MMA toxicity following airborne exposure

(see below). It has been demonstrated that toxicity at this site is dependent on local metabolism of MMA by carboxylesterases, producing methacrylic acid.[SCOEL4] In vitro studies have shown that carboxylesterase activity (V_{max}) in samples of morphologically normal human nasal epithelium, obtained from 5 individuals undergoing craniofacial surgery, was much lower than in rat nasal epithelium. For the olfactory region, the carboxylesterase activity was thirteen fold lower in human samples than in rat; and for the respiratory region it was six fold lower in the human samples than in rat. Another difference is in the distribution of carboxylesterases, which in human nasal epithelium are widely dispersed, whereas in the rat carboxylesterases are concentrated in the olfactory submucosa and Bowman's glands.[SCOEL4]

Andersen et al. (2002)[SCOEL5], using data from Mainwaring et al. (2001)[SCOEL4], created a physiologically-based pharmacokinetic (PBPK) model to determine the nasal tissue dosimetry of methacrylic acid following MMA exposure. It was predicted that, for a given airborne exposure to MMA, nasal olfactory epithelium tissue concentrations of methacrylic acid would be three fold lower in humans compared with rats if the esterase distribution in humans was similar to rats, or eight fold lower in human tissues if it is assumed that, in contrast to rats, human esterases are distributed evenly throughout the epithelial layer. Previous modelling attempts estimated a similar dosimetric adjustment of between 2.4 and 4.76, operating in the direction of a lower nasal epithelium concentration of methacrylic acid in humans than in rats, for a MMA concentration range of 1-400 ppm.[SCOEL6,SCOEL7]

4.4 Elimination

As already mentioned in Section 5.3, elimination of MMA is rapid and complete. After hydrolysis of MMA and subsequent conjugation with Coenzyme A, the degradation follows the same pathway as the amino acid valine (see figure 1).

Within 2 h 65% of the administered dose was expired as $^{14}CO_2$ by rats, irrespective of the route of administration. After 10 days 88% of the dose was expired (Bratt and Hathway 1977). Detailed information on the various excretion products is presented in Table 3.

Crout et al. (1982) found similar results after ip injection into two rats. After 4 h ca. 72% and after 24 h ca. 85% of the dose was recovered as $^{14}CO_2$. The percentage of radioactivity recovered in the urine was 14.5 and 7% respectively.

The half-life time of MMA in blood in vitro at 37°C lies in the range of 20 - 40 min (independent of age or sex, n= 10). The initial concentration was 10 µg/

ml (Corkin et al. 1976). The in vivo half life time was 47-55 min. MMA was measured in central venous blood of nine patients undergoing total knee arthroplasty. The highest concentration ranged from 0.10 to 1.44 µg/ml (Svartling et al. 1986).

Even after high exposures, that is, when MMA polymerises into polyMMA for the fixation of prostheses in orthopedic surgery, MMA and methacrylic acid were only detected in blood, not in urine. Concentrations of MMA ranged from 0 to 15 µg/ml, for methacrylic acid it ranged from 0 to 6.1 µg/ml (Crout et al. 1979).

4.5 Biological monitoring

Although MMA is rapidly metabolised, low levels can be found in the urine after exposure to relatively high concentrations. Unexposed persons excrete less than 15 nmol MMA per mmol creatinine. No quantitative data are available on the relationship between exposure and internal or excreted dose (Rajaniemi et al. 1989).

Methylmalonic acid is a degradation product of MMA. It is normally excreted in the urine in very small amounts and is often below the limit of detection. When MMA is metabolised through hydrolysis the concentration of methylmalonic acid rises, but is still very low.

In GC systems it is usually eluted with a retention time identical, or almost identical to that of 3-hydroxy-3-methylbutanoic acid (ß-hydroxyisovaleric acid), with which it may easily be confused (Crout et al. 1982).

Table 3 Excretion and retention of radioactivity in rats after administration of methyl-[^{14}C]methacrylate (Brat and Hathway 1977).

form of ^{14}C label	route of administration	dose (mg/kg)	recovery of ^{14}C (% of dose)[a]					
					exhaled gases			
			urine	faeces	$^{14}CO_2$	unchanged ^{14}C MMA	carcass plus skin	total
Methyl[1,3-^{14}C]-propylene-2-carboxylate	by stomach tube[b]	5.7	4.7	2.7	88.0	0.1	4.1	99.6
	i.v.[b]	5.7	6.6	1.7	84.0	0.7	6.6	99.6
Methyl[2-^{14}C]-propylene-2-carboxylate	i.v.[b]	6.8	7.2	1.8	84.1	1.0	6.6	100.7
	by stomach tube	120.0	6.0	3.0	76.4	1.4	[c]	

[a] 10 days after administration
[b] data are representative of that obtained in several animals
[c] not measured

4.6 Summary

MMA is absorbed through the skin by animals and humans. Absorption through rat tail amounted to 22 $mg.cm^{-2}.h^{-1}$, measured with a method which can easily lead to overestimation. The maximum absorption rate in vitro through human skin amounted to 274 $\mu g.cm^{-2}.h^{-1}$ in the occluded situation and to 107 $\mu g.cm^{-2}.h^{-1}$ in the unoccluded situation.

Both after intravenous injection and oral administration MMA is rapidly distributed over the body.

MMA appears to be metabolised through the same pathway as the amino acid valine. The first step is hydrolysis by carboxylesterase into methacrylic acid and methanol. At low concentrations the in vitro half-life time of MMA is 20 - 40 min (measured in human blood) and the in vivo half-life time is 47 - 55 min (measured in surgical patients). High doses of MMA saturate enzymatic hydrolysis and unchanged MMA is thus conjugated to glutathione. GSH depletion occurs mainly in the liver and to a lesser extent in the kidneys and thioethers are excreted in the urine. A single dose of 2 g/kg i.p. injected into rats increased thioether excretion. BIocking carboxylesterases also increases thioether excretion, even when low dosages of MMA are administered.

In the case of vitamin B_{12} deficiency methylmalonic acid is excreted in the urine, which amounted to approximately 1% of the administered dose in one person.

Elimination of MMA is mainly by expiration of CO_2. In rats within 2 h 65% of the administered dose is expired, within 10 days 88% is expired, both after intravenous injection and oral administration. About half the remainder of the dose is excreted in the urine and the rest is retained by the body tissues. Pulmonary excretion of unchanged MMA accounted for less than 1.0% of the dose.

Additional data in SCOEL document

In experimental animals, absorption of MMA is almost complete after oral administration. Of inhaled MMA vapour, 10-20% was deposited in the upper respiratory tract in a study with rats. Much of the dose probably passes quickly into the epithelial lining along the length of the respiratory tract.

According to the SCOEL, following airborne exposure, the nasal epithelium (particularly the olfactory region) is a primary site of MMA toxicity. Toxicity at this site is dependent on local metabolism of MMA by carboxylesterases to methacrylic acid. It was shown that carboxylesterase activity in human nasal epithelium is much lower than in rat nasal epithelium (thirteen fold for the olfactory region and six fold for the respiratory region). Using a PBPK model, the nasal olfactory epithelium tissue concentration of methacrylic acid following MMA exposure was predicted three to eight fold lower in humans, compared with rats.

Chapter 5

Effects*

5.1 Observations in man

5.1.1 Irritation and sensitisation

General

MMA can be irritating to skin, eyes or mucous membranes and can cause allergic dermatitis or stomatitis. Apparently man is more sensitive in this respect than the animal species tested. The allergic dermatitis is characterised as itching, with erythema, oedema and vesiculation followed by eczema and unique and consistent paresthesia. In some cases tenderness is observed outlasting the duration of the eruption (Borchard 1981).

Cases of individuals exposed to MMA

In total 9 cases are described in 7 studies. The studies are: Pickering et al. 1986, Losewicz et al. 1985, Kassis et al. 1984, Condé-Salazar et al. 1986, Kanerva and Verkkala 1986, Nissen and Corydon 1985 and Scolnick and Collins 1986. The

* Text cited from the advisory report by the Health Council published in 1994 (1994/09). Conclusions made in 1994 not necessarily mean that these are adopted presently by the DECOS. Additional data from the SCOEL document and other published data are presented in italic.

overall conclusion is that MMA can be irritating to the skin, eyes and mucous membranes; in some individuals it can cause asthmatic and sensitisation reactions.

The case studies can be summarised as follows.

With reference to *occupation*: eight of the nine cases developed symptoms while mixing bone cement and one manufactured, applied and painted artificial nails and wore artificial nails herself. Three of the eight cases were dental technicians, three operating room nurses and two female nurses.

With reference to the *symptoms:* dermal allergy developed in the woman handling artificial nails (Condé-Salazar et al. 1986), in two dental technicians (Kanerva and Verkkala 1986) and two female nurses (Kassis et al. 1984). In the two dental assistants dermatotoxic and neurotoxic effects were observed in biopsies from positive patch tests.

Table 4 Environmental MMA concentrations in air (mg/m^3) resulting from mixing of polymeric cement on open trolley (Pickering et al. 1986).

time (sec)	procedure	conc. of MMA (mg/m^3)
0	breakage of phial	0
15	addition of liquid cement	520
30	mixing	1,140
45	mixing	1,560
60	mixing	680
75	spoonful of cement removed from bowl	520
105	bowl cleaned out	330

Asthmatic reactions were observed in one dental technician (Losewicz et al. 1985) and one operating room nurse (Pickering et al. 1986). The two remaining cases developed rather unusual symptoms which cannot be well explained: one operating room nurse developed a corneal ulcer (Nissen and Corydon 1981) and one operating room nurse developed bifrontal headache, a sensation of heaviness in arms and legs, lightheadedness and a sense of extreme lethargy (Scolnick and Collins 1986).

With reference to *exposure levels:* Only in three cases were the air levels of MMA measured. The study by Pickering et al. (1986) was the most elaborate one. The results are described in Table 4. The peak concentrations of MMA occurred during the first 90 seconds of mixing. Although the time-weighted average did not exceed the TLV of 410 mg/m^3, brief but repeated exposure to high peak concentrations of MMA occurred. Very low levels of MMA of in the order of 2 to 6 mg/m^3 were measured in the two unusual cases (the corneal ulcer

and the CNS symptoms), (Nissen and Corydon 1985, Scolnick and Collins 1984).

For the cases with dermal allergy the air levels of MMA are less relevant. The handling of a polymerising MMA product with bare hands implies exposure to varying concentrations of MMA. MMA can even penetrate through one or two layers of latex gloves (Kassis et al. 1984).

Other case studies

Several cases of allergy have been found in the literature.

A 28-year old woman developed contact dermatitis wearing an above-knee prosthesis. She reacted positively to a patch test with 2% MMA, 2% triethyleneglycoldimethacrylate and two brands of resin (Foussereau et al. 1989).

A 58-year old prosthetic dental technician developed generalised sensorimotor neuropathy. This neuropathy may be associated with 30 years of occupational cutaneous and inhalational exposure to methylmethacrylate (Jacob and Donaghy 1991).

A 42- and a 59-year old woman showed allergic contact stomatitis in their mouth after wearing a dental prosthesis. They had a positive reaction in a patch test with 2% and 25% MMA (Corazza et al. 1992, Ölveti 1991).

Between 1974 and 1992 four dental workers who had developed occupational allergic contact dermatitis from working with dental. prostheses consulted a dermatologist of the Section of Dermatology. All patients had positive allergic patch test reactions to MMA (1-10%). Some patients also reacted positively to other acrylates and methacrylates (Kanerva et al. 1993).

Three cases of asthma caused by occupational exposure to MMA are described by Savonius et al. (1993a and b). They were diagnosed in a group of 3,152 patients examined between 1985 and 1991. The persons were: a 48-year old female, working as a plate engraver and using MMA glues occasionally; a 32-year old male, assembling hearing devices and using MMA in the manufacture of earplugs; and a 46-year old female dental technician, preparing dental fillings.

Additional information*

Two cases of dental technician trainees (females, aged 20 and 24 years) were diagnosed for hypersensitivity pneumonitis due to inhalation of MMA, who were

* Data retrieved up to October 2011 and not mentioned in any of the two advisory reports.

exposed for a few weeks. Exposure levels are not reported. Other causes (i.e., pneumoconiosis to mineral or metal particles) were excluded in view of the duration of exposure. Symptoms upon hospitalisation included severe dyspnoea and cough. Blood analysis revealed hypoxemia. Lung capacity (FVC) was 50% and 65% of predicted. One individual was subjected to a provocation with a MMA aerosol, upon which the clinical symptoms reappeared.[10,24]

Cross sensitisation

Three patients employed in electronic assembly operations had allergic contact dermatitis to polyethylene glycol dimethacrylate, found in an anaerobic sealant. No cross reactions to MMA were observed on patch testing (Mathias and Maibach 1984).

Surveys of groups exposed to MMA

The irritative properties of MMA to the skin are well-known. Allergic reactions are also frequently described, although the incidence varies. The description of the symptoms is sometimes ambiguous, hindering therefore the diagnosis. Repeated contact with MMA, frequent hand washing and occlusive exposure enhance the skin reactions. Several surveys on groups of persons exposed to MMA or a polymerising product have been performed: two studies used questionnaires and the rest used the patch test.

The frequency of the dermal allergic and irritation reactions as found in the studies is summarised in Table 9.

The following can be concluded:

With respect to dermal allergy: The larger studies show an incidence of 2 to 15%. Exposure is either occupational or non-occupational: dental technicians handle the polymerising product with their bare hands and patients with polyMMA dentures come into contact with residual monomer. The high incidence of allergic reactions found in the other studies is probably due to selection of the test group or due to the use of 100% MMA as a test solution.

The allergy is described as a contact dermatitis with erythema and itching.

With respect to dermal irritation: dermal irritation varies from ca. 18% in occupationally exposed persons to 1-50% when patch tested with various solutions of MMA. The symptoms are described as contact eczema, dermatitis or mild erythema.

Respiratory allergy

Allergic respiratory reactions have been described in a group of dental students as a result of exposure to volatile MMA (Andrews et al. 1979). The study the pulmonary effects of MMA vapour exposure in a group of 77 dental students. The past histories and symptoms associated with usual laboratory activities of 502 dental students were determined by a multiple-choice questionnaire. Of those students exposed, 6% reported respiratory symptoms with MMA and 5% while working with high-speed drills. Less than 1% reported symptoms with other materials. 88 percent of students reporting MMA sensitivity had histories of either asthma or allergic rhinitis. Spirometry was performed before and after a controlled exposure to MMA in subsets of individuals representing normals, asthmatics, those with allergic rhinitis, smokers and those students who reported symptoms on usual exposure. The concentration of MMA in the air is not given. There was no significant change in spirometry or symptoms among the 77 students tested.

It is concluded that about 8% of dental students experience work-related acute respiratory symptoms, MMA exposure and high-speed drilling are most often associated with symptoms, and most symptomatic individuals have prior histories of asthma or allergic rhinitis. Differences in conditions between the controlled test setting and the student laboratories, including higher vapour concentrations and the presence of finely ground particulate acrylic material in the student laboratories, may account for the failure to elicit airway responses during controlled exposure.

Penetration through gloves

In order to prevent dermal contact with MMA, the use of gloves is advised.

The disadvantages of the use of gloves are: hindered manual handling and, depending on the material of which the glove is made, penetration of MMA followed by occlusive exposure.

MMA penetrated disposable rubber gloves (Pegum and Medhurst 1971) and 5 latex, 1 polystyrene-butadiene and 1 polychlorobutadiene gloves (Waegemaekers et al. 1983). On the other hand, breakthrough times longer than 3 h were measured for butyl and teflon gloves (Johnson and Anderson 1990).

Table 5 Summary of the frequency of dermal reactions found in group surveys.

reference; surveyed group	type of test	number of persons	occlusive exposure
Estlander et al. (1984) dental technicians	questionnaire	106	no (98%)
Rajaniemi and Tola (1985) dental technicians	questionnaire	202	no (81%)
Spealman et al. (1945) medical students	patch (100%)	50	no exposure
Fries et al. (1975) handlers of bone cement	patch (10% sol.)	13	not given
Borchard (1981) handlers of bone cement in operation theatres	patch (10% sol.)	13	yes
Axéll (1983) suspected allergy to dentures	patch (10 and 1% sol.)	199	yes
Pevny and Binzenhöfer (1984) suspected allergy to dentures	patch (30% sot.)	132	yes
Condé-Salazar et al. (1988) sealants in car factory, engineering and electronic industry	patch (10% sol.)	6	no
Rudzki et al. (1989) 333 nurses, 92 dentists and 167 physicians	patch (1% sol.)	592	for dentists: not given. Others: no exposure
Guerra et al. (1993) patients suspected of occupational acrylic sensitization	patch (5% sol.)	82	not given

Table 5 Continued.

dermal irritation		dermal allergy	
frequency	symptoms	frequency	symptoms
19% (n = 20)	irritant contact eczema	15% (n = 16)	atopic dermatitis
17% (n = 34)	dermatitis	2% (n = 4)	not described
50% (n = 25)	mild erythema	20% (n = 10)	erythematous, itching areas
23% (n = 3)	dryness and fissuring	54% (n = 7)	itching, erythema, oedema and vesiculation
	not described	54% (n = 7)	contact dermatitis (itching, erythema, oedema)
1 and 2% (n = 2 and 4)	not described	2.5 and 5% (n = 5 and 10)	not described
		3% (n = 4)	not described
	not described	54% (n = 3)	contact dermatitis
	not described	<0.2% (n = 1 dentist)	not described
	not described	1.2% (n= 1)	contact dermatitis in hands, forearms and face

Gloves made of viton-butyl rubber 0.27 mm thick, were impervious for 15 minutes. And a three-layered PVP glove, 0.07 mm thick, consisting of an outer layer of polyethylene, an intermediary layer of ethylene vinyl alcohol copolymer and an inner layer of polyethylene, was impervious for 20 min. No macroscopic changes were observed in the glove after 6 hours' immersion in concentration MMA (Darre et al. 1987b).

Additional data in SCOEL document

Irritation
Based on both experimental animal and human data, liquid MMA can produce irritation of both the skin and the eyes on direct contact.[SCOEL8] Some eye irritation has been reported in humans with exposure to airborne MMA; a clear dose-response curve for this effect has not been reliably established, although the threshold concentration would appear to be above 100 ppm. Similarly, symptoms of sensory irritation of the upper respiratory tract have been reported in workers exposed to airborne MMA; as with eye irritation, the threshold for sensory irritation of the respiratory tract has not been reliably established but would appear to be above 100 ppm.[SCOEL9, SCOEL8]

Sensitisation
MMA is clearly a skin sensitizer. There are numerous case reports of skin sensitisation to MMA in certain occupational situations, where frequent and prolonged unprotected skin contact with monomer-containing preparations was common practice. Single cases of skin sensitization were also reported in some medical and cosmetic applications.[SCOEL8]

Additional information*

Jaakkola et al. (2007) performed a cross-sectional study on the respiratory effects of exposure to methacrylates among female dental assistants (N=799).[13] Daily use of methacrylates (not further specified) was statistically significantly related to an increased risk of adult-onset asthma, nasal symptoms, and work-related cough or phlegm. Furthermore, increased frequencies of respiratory hypersensitivity among dental personnel was observed using challenge testing, and IgE positivity tests.[21] In addition, two cases (nail technicians) of work-related occupational asthma were reported, using bronchial provocation tests with methacrylates.[23] In none of the three studies exposure levels were measured. Furthermore, none of the studies reported on MMA-exposure only.

The permeability of MMA of dental and industry gloves was determined in a recent study. Vinyl gloves displayed the maximum permeability to MMA(57.78 µL/mL at 30 minutes), followed by latex (43.50 µL/mL at 30 minutes), and neoprene industrial gloves (5.58 µL/mL at 30 minutes). Neoprene industrial

* Data retrieved up to October 2011 and not mentioned in any of the two advisory reports.

gloves remained impervious for over 25 minutes. Vinyl and latex gloves were permeable to MMA from the first minute. It is concluded that clinical gloves do not provide protection against dermal exposure to MMA.[26]

5.1.2 *Acute toxicity*

No data have been found.

Additional information

Muttray et al. (2007, abstract only) reported on the absence of irritation in the nose of twenty healthy volunteers.[19] The volunteers were exposed to 50 ppm MMA for four hours, after which nose secretion was sampled for analyses on the levels of interleukins. Furthermore, no changes in mucociliar transport time and odour threshold of n-butanol have been found, when data were compared before and after exposure.

5.1.3 *Short-/long-term exposure*

The main effects of MMA concern the CNS (Pagniano et al. 1986, Froines and Garabrant 1986; further a Russian study, described by the following authors: IARC 1979, Innes and Tansy 1981 and NTP 1986; several other Russian studies are described by DFG 1984). Also, occupational contact to MMA reportedly decreases nerve conduction velocity locally (Seppäläinen and Rajaniemi 1984 and Rajaniemi 1986). A study on the olfactory function was performed by Schwartz et al. (1989).

The CNS disturbances found in the above mentioned studies are described as headache, pain in the extremities, nausea, loss of appetite, fatigue, sleep disturbances, irritability and loss of memory. Other symptoms described (summarised by DFG 1984) are changes in blood parameters and in lipid, hormone and iodine metabolism. The dose range was either very wide (2 to 208 mg/m^3), incompletely given, or not given. Therefore, no dose-response relationship can be established. Furthermore, in most cases no control groups were included.

The only study with some information on exposure is the one by Pagniano et al. (1986). Vapour concentrations were measured when 147 dental students were constructing acrylic trays containing MMA. The concentrations of MMA vapour ranged from 6.7 to 68.2 mg/m^3 (environmental monitoring; 6 sampling times

during 5 hr). The average ranged from 12 to 55 mg/m^3. A control group was not included. Survey results showed that the most prevalent symptoms were of transient nature and consisted of headache (53%), dizziness (51%), and sinus irritation (36%). These were followed, in decreasing order, by irritation to skin, loss of concentration, breathing difficulty, hunger, nausea, coughing, irritation to eyes and tachycardia.

Froines and Garabrant (1986) measured the exposure to MMA in nailshops (see Table 1, Section 5.2.2), but did not link these data with the CNS complaints of the manicurists.

Nerve conduction velocity was measured in a group of dental technicians selected from a questionnaire study by Rajaniemi and Tola (1985). The results are described in two studies (Seppäläinen and Rajaniemi 1984 and Rajaniemi 1986). Nineteen cases had complained of neurological symptoms like coldness, numbness, whitening or pain in the finger exposed to MMA. The study group consisted either of 20 or 15 righthanded subjects. An age-matched control group was also tested.

The sensory conduction velocities of finger nerves of the dominant hand were reportedly slower both when the exposed group was compared with the control group and also when within the exposed group the dominant hand was compared with the non-dominant hand. The decrease was correlated with the feeling of numbness. These findings are considered to represent mild axonal degeneration on the areas with the closest and most frequent contact with MMA. Frank axonal neuropathy was suspected only in two cases. The neurophysiological findings did not correlate with current dermatitis; however, they were more common among those with a longer and/or heavier exposure.

Lindberg et al. (1991) measured the conduction velocity in several nerves in ten floor-layers, who were occupationally exposed to MMA. Also the lung function was measured with several tests. Psychophysiological complaints were scored by means of a computerised questionnaire. For exposure data see Section 5.2.2. The exposed persons had twice as much psychophysiological complaints as a control group of 10 persons of comparable age. The complaints consisted of irritation of the mucous membranes, effects on the CNS, neurasthenia and general-somatic complaints. No effort was made to relate the complaints to the duration of exposure or the age of the floor-layers. The conduction velocity was diminished in the *N. suralis* (from foot to underleg), the more so in the N. medianus (underarm) compared to normal values obtained from a former study with an unknown study group, probably persons from the general population.

Again, no correlation is given between the conduction velocity and the duration of exposure or the age of the floor-layers.

Lung function, measured as maximal voluntary ventilation, vital capacity, forced vital capacity, forced expiratory volume in the first second and maximal airstream during several phases of expiration, was normal. The floor-layers had to perform the tests on their own, three times per day. Only five of the ten complied with the procedure.

Marez et al. (1992) studied the possible cardiotoxic effects among workers. Twenty-two asymptomatic exposed workers in two factories of polyMMA manufacture and 18 persons not exposed to MMA were monitored for 8 h for heart activity with an ambulatory Holter system. At the same time atmospheric levels of MMA were monitored. The overall 8-h average air concentration of MMA in the two factories was essentially the same: 77 and 90 mg/m^3, respectively. The range of measured 8-h concentrations was 37-133 mg/m^3 and 49.5-160 mg/m^3, respectively. The study did not support the hypothesis that MMA is responsible for cardiomyodystrophy. However, supraventricular and ventricular ectopic beats were significantly more frequent among exposed workers versus controls ($p<0.01$). Moreover, depolarisation changes such as large T waves were noted only in exposed workers (eight cases against none in the control group). Although there was no clear relation between MMA exposure and the recorded cardiac changes in the exposed group, the role of MMA cannot be totally excluded. In the same two factories, 1-hour peak exposure levels between 474 and 1664 mg/m^3 (114-400 ppm) were measured (Marez et al. 1991). The possibility that the clinical findings are caused by (repeated) exposure to peak concentrations is not discussed by the authors.

In a group from the same worker population bronchial symptoms were monitored by means of a questionnaire and the respiratory function was measured by means of spirometry (Marez et al. 1993). The exposed group consisted of eight workers with more than 5 but less than 10 years exposure and 32 workers with more than 10 years exposure. They worked in two factories where the overall mean atmospheric concentrations of MMA were 77 and 90 mg/m^3 with ranges of 37-133 and 49.5-160 mg/m^3 and with 1-h peak concentrations between 474 and 1664 mg/m^3. The control group consisted of 45 workers never exposed to MMA or any other respiratory irritant. In the exposed group 20% had chronic cough compared with 1% in controls. Spirometric values at the beginning of the workshift were similar in both groups, but a mild airways obstruction appeared during the workshift. The maximum expiratory flow when 50% of the forced vital capacity remained to be exhaled (MEF_{50}) and the ratio of MEF_{50} to maximal expiratory flow (MEF_{50}/MEF) decreased significantly during

the workshift among exposed workers vs controls (p = 0.04 and 0.01, respectively). Results remained unaffected after adjustment for smoking. It can be concluded that exposure to MMA seems to be responsible for a mild airways obstruction but further study on a large population would be useful.*

Schwartz et al. (1989) investigated the olfactory function of 731 workers at a chemical facility which manufactures acrylates and methacrylates. The current ethylacrylate and acrylic acid levels varied from 0.01 to 56 ppm; levels of MMA were not given. The test consisted of scratching a pencil tip over an odorant label strip to release the fragrance, smelling the label, and choosing the perceived odour from four multiple choice answers. In a cross-sectional analysis of the data, no associations of chemical exposure with olfactory test scores were observed. In a nested case-control study a dose-response relationship was found between olfactory dysfunction and cumulative exposure scores. The data also revealed decreasing exposure odds ratios with increasing duration since last exposure to these chemicals, suggesting that the effects may be reversible. However, the results cannot be ascribed to MMA alone, since exposure levels of MMA were not given and the workers were also exposed to other acrylic compounds.

5.1.4 *Epidemiological studies*

From the described epidemiological and long-term studies it can be concluded that CNS-symptoms and dermal problems are common complaints of people working with MMA. Changes in several blood parameters are also reported. However, a dose response relationship cannot be established.

In the mortality studies no excess was found in all-cause or cause-specific mortality. Only with exposure to high levels of MMA in combination with high levels of ethylacrylate and by-products of the polymerisation process was an increase in colon cancer found.

Four studies are available: two mortality studies (Collins et al. 1989 and Walker et al. 1991), and two on CNS-symptoms and changes in blood parameters (IARC 1979 and Cromer and Kronoveter 1976).

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* Note (February 2011): The Committee re-evaluated the findings of Marez et al. (1993), and noted several flaws. For example, the only changes observed after spirometry was decreased MEF_{50} and MEF_{50}/MEF, whereas the most relevant parameters, FEV_1 and FEV_1/FVC did not show a difference between the exposed and non-exposed group. Furthermore, no personal air monitoring data was presented, and the observed effects may have been related to peak exposures. See also Part one in this report.

IARC (1979) described a report (the original is not available) on 152 workers exposed for years to 2-200 mg MMA/m^3. One hundred nineteen complained of headache, 45 noted pain in the extremities, 32 showed excessive fatigue, 32 had sleep disturbances, 30 had loss of memory and 25 showed irritability. A majority of workers had been employed for 10 or more years. DFG (1984) report about this study that the authors also observed an increased leucocyte count and a trend towards erythrocytosis with macrocytosis, a change in K-Ca ratio and a change in cholinesterase-activity in the majority of the 152 workers. These data are from a Russian study, no more data are available.

The study by Cromer and Kronoveter (1976) has two parts: a screening and a comprehensive survey.

In the screening survey employees of 27 establishments were studied for health effects potentially resulting from exposure to MMA vapours. These varied from monomer production and lens manufacturing facilities to dental laboratories. MMA concentrations are specified for each job category, and lie between < 20 mg/m^3 and 540 mg/m^3 TWA 8 h (two personal air samplers were used in 8 hr). From approximately 350 questionnaires returned (of the 552) it could be seen that the complaints, primarily referable to MMA exposure were eye and upper respiratory tract irritation, headache, light-headedness (a feeling of being high), and skin rash or burn. These symptoms usually occurred during MMA spills, when levels of MMA were likely to be high. The prevalences of complaints referable to the cutaneous (19%), respiratory (30%) and urogenital systems (25%) were noteworthy, although respiratory complaints came nearly all from individuals who had a history of smoking. No control group was present for comparison. With reference to the genitourinary complaints the authors mention that these data come from self administered questionnaires, often lacking in pertinent detail. Moreover, lack of exposure data make these findings tenuous.

Subsequent evaluation focused on these indicative complaints.

A group of 67 of these MMA exposed workers and 61 controls underwent three serial complete blood cell counts over a period of several years. No differences were noted in haemoglobin levels or differential count values. A significant difference ($p < 0.002$) was noted in mean white blood cell count values: mean value of 8.44 x $10^3/mm^3$ for exposed, and 7.78 x $10^3/mm^3$ for nonexposed.

On the basis of the screening survey a comprehensive survey was carried out at five cast sheet manufacturing facilities. Although the authors suggested that effects in several blood parameters and on the CNS occurred after exposure to

MMA, especially in the job categories with higher exposure, the following imperfections in study design prevent the establishment of a dose-response relationship:

- In one of the sheet plants both MMA and ethylacrylate were within measurable quantities; in all plants a large variety of additives was used in small amounts. No remark was made what the effect is of combined exposure; it was stated that the predominant exposure is to MMA.
- Of a total of 169 workers in the five plants 91 cooperated in the survey. The group with the highest exposure (four distillers, mean exposure 366 mg/m^3) did not volunteer for the study. Further, no information is given concerning which persons in what job category withdrew from the survey.
- The 91 persons were divided into four groups, according to exposure level. In group one were combined the persons which were currently exposed to less than 21 mg/m^3 and those with less than 2 months of exposure. These two groups are in fact incomparable and therefore cannot be combined. Together with the three other exposure groups (two current and one past exposure group) the division leads to a small number of persons per exposure group, therefore the increase in effects found is not statistically significant. No mention is made what job category is represented in each exposure group.
- The control group, which was not different from the exposed groups concerning age, sex, race or smoking history, consisted in one case of 43 persons, in other cases of 41 or 35 persons. Further, in each group several persons did not volunteer for the blood tests.
- Environmental monitoring at the various work areas by means of personal air sampling (sampling time between 4.7 and 7.2 hr) revealed a large variation in exposure and a high standard deviation. Furthermore, apart from the group of four distillers, in two of the four factories the group of mold fillers was the highest exposure group, and in the other two factories the group of mix men was the highest exposure group. For the fifth plant only the total number of employees was given. Therefore, a classification into exposure groups according to job category was impossible.

Collins et al. (1989) studied the mortality pattern in a group of 1561 workers exposed to MMA. Exposure estimates ranged from 0 to 48 mg/m^3 (mean: 0.5 to 4 mg/m^3). Two hundred thirty-seven death certificates were evaluated: 123 from the non-exposed group and 114 from the exposed group. No statistically significant excess was found in all-cause or cause-specific mortality. However, due to the low exposure concentrations MMA-associated deaths are not expected.

Walker et al. (1991) studied the mortality from cancer of the colon and rectum in three cohorts exposed to ethyl acrylate and MMA. The cohorts worked in 1933-1982 in two plants manufacturing and polymerising acrylate monomers. In the early years ethylacrylate was used in a quantity of 12% of the polymerising mixture. From 1943 on changes in production methods resulted in a decline to zero in the use of ethylacrylate in acrylic sheet production. Therefore, it can be concluded that MMA and not ethylacrylate was the chemical to which exposure occurred.

The three cohorts consisted of 2524, 6548 and 3381 men. The cohorts were analysed in three ways. One divided the workers in four cumulative dose groups. The other used a division in six categories of maximum achieved exposure levels. And third, the workers were separated according to the year in which they were hired.

In dividing the workers in cumulative dose groups there was no indication of an elevated risk for colon cancer at lower levels of exposure, for which the accumulated experience was substantial. In the high exposure categories there were insufficient amounts of person-time to conclude an increased risk for colon cancer. The rate of rectal cancer was much lower than for colon cancer, therefore, the results are more imprecise.

When the workers were divided according to maximum achieved exposure levels there was no indication of a regular increase in relative mortality due to colon cancer.

When the workers were divided according to date of hire it was found that the two cohorts with later dates of hire showed no excess mortality. In the earliest cohort excess colon cancer seemed restricted to men employed extensively in the early 1940s in jobs entailing the highest exposures to ethylacrylate and MMA and volatile byproducts of the polymerisation process. The excess mortality appeared only some two decades after the equivalent of three years employment in jobs with the most intense exposures.

Additional data in SCOEL document

In a cross-sectional study conducted in the UK, workers at three factory sites producing poly-MMA sheets were assessed (Pickering et al. 1993; unpublished report). SCOEL10 Based on workplace station measurements, the workers were divided into three exposure level groups: low (< 1 ppm 8-h TWA), medium (5 ppm 8-h TWA) and high (20 ppm 8-h TWA). However, it was also predicted that the personal exposures at this factory would be similar to that of the study of Pausch et al. 1994SCOEL9 (see below), indicating that a significant proportion of

workers would have been exposed to an average concentration of 50 ppm (8h TWA). In addition, a significant proportion of the workers self-reported daily exposure to transiently high levels of MMA as a result of 'cell bursts' or spills; such events have been shown to create transient peaks of several hundreds of ppm (up to 500 ppm).

The results showed a low prevalence of respiratory symptoms among the workforce with no indication of an exposure-response relationship. The results of spirometry tests showed no exposure-related changes and any differences from expected values were so small as to be of no functional significance. Overall, there were no significant respiratory health effects in this worker population, a significant proportion of whom were thought to have had average exposures of approximately 50 ppm (8h TWA).

In another worker survey, a questionnaire study and visual examination of the nasal cavity was performed over a 2-year period on 211 workers at a poly-MMA sheet production factory in Germany (Pausch et al. 1994; unpublished report; not available to the SCOEL).[SCOEL9] Working areas were classified into the following 8h TWA exposure ranges (as geometric means) of 3-10 ppm (7 people), 10-20 ppm (128 people), 20-30 ppm (20 people) and 30-40 ppm MMA (56 people). However, about one third of the measurements in the higher exposure category exceeded 40 ppm (up to 50 ppm; and were beyond 50 ppm in 15% of cases).

Small numbers of workers reported respiratory symptoms of “mild” to “moderate” severity; these included impaired nose breathing (6/211), dry nose (6/211), rhinitis (1/211), reduced sense of smell (2/211), eye irritation and lacrimation (3/211) and chronic bronchitis (2/211). The only findings that showed any clear evidence of an association with MMA exposure were those indicative of transient eye and nose irritation, which correlated with short-term peaks of peak exposure (airborne concentrations somewhere between 100 and 680 ppm for periods of 5-15 minutes duration). There were no abnormalities of the nasal cavity in this workforce.

Additional information*

A critical review of the epidemiological literature on potential cancer risks from MMA focused on cast acrylic sheet manufacturing workers. Excesses of respiratory and stomach cancers, observed in some cohorts of workers exposed to MMA, were attributed to lifestyle exposures such as cigarette smoking or diet.

* Data retrieved up to October 2011 and not mentioned in any of the two advisory reports.

An excess of colorectal cancer in one group of workers exposed to high levels of MMA during the 1930s and 1940s remained unexplained. The authors concluded that there is insufficient evidence that MMA is a human carcinogen, based on the lack of consistency of the various studies, the absence of dose-response relationships and the lack of support from studies in animals.[27]

Exposure to MMA and total dust, as well as workers' health symptoms (by questionnaire), were investigated in twenty dental laboratories in Tehran, Iran. Time-weighted average (8h-TWA) of MMA for technicians with direct and indirect exposure were 327 ± 79 and 283 ± 42 mg/m^3, respectively. Peak concentrations (5-15 min) were 337 ± 37 and 329 ± 45 mg/m^3, respectively. Cough and skin dryness were the common health symptoms. Dryness of skin (especially in hands) was associated with MMA concentration ($p = 0.03$). The prevalence of respiratory symptoms among technicians with direct exposure was 18.4% for cough, 23.7% for phlegm, and 42.1% for asthma. There was a significant difference between smokers or individuals with a history of asbestos exposure and non-smoking individuals without an asbestos exposure background. In view of the high proportion of smokers (92.9%), and asbestos-exposed individuals (41.9%) in this study, it is concluded that these factors were largely responsible for the prevalence of respiratory symptoms.[9]

A study was carried out on 104 employees of a MMA/polymethyl methacrylate (PMMA) production facility in Bulgaria. The control group consisted of 55 healthy employees not working in chemical operations at the plant. Airborne monitoring was conducted over a 10-year period (1983-1993) for MMA and the precursor chemicals methanol and acetone cyanhydrine at the MMA operation, and MMA was monitored at the PMMA operation (potential exposure to this chemical only). Acid-base status of the workers was evaluated (pH, pCO_2, pO_2 and HCO_3 in plasma). Data from retrospective monitoring of air levels of the chemicals were compared with the acid-base status of workers at the plant. MMA exposure was highest in the PMMA plant and ranged between 24 and 94 mg/m^3. In this plant, 8 to 31% of the samples exceeded 50 mg/m^3. Acid-base disruption, indicated by reductions in plasma pH, pO_2 and HCO_3, was found for all groups except the control population. The greatest reduction was associated with PMMA production workers (n=13): pH, 7.3±0.02 / 7.4±0.02 mmHg; pCO_2, 36.3 ± 6.03 / 41.5 ± 6.8 mmHg; pO_2, 36.3 ± 6.03 / 41.5 ± 6.8 mmHg; HCO_3, 18.3 ± 4.0 / 23.7 ± 1.9 nmol/L in exposed/control subjects ($p < 0.05$).[22]

Muttray et al. (1997) performed a cross-sectional study on the prevalence of smell disorders among 175 MMA-exposed workers and 88 non-exposed workers from a same German acrylic sheet production facility. The duration of exposure varied between one and thirty-three years. Compared to controls and using the Rhino-Test®, a smell test, the authors did not find relevant olfactory disorders with chronic exposure to MMA at a concentration of up to 50 ppm, including peak exposures (on average between 100 and 300 ppm). No adjustments were made for smoking habits, whereas the Committee noted the high percentages of smokers among the participants (58% in the exposed group; and 34% in the control group). Also no pathological examinations on the nose tissue have been carried out, and no statistical analyses have been performed.

5.2 Animal experiments

5.2.1 Irritation and sensitisation

Irritation

The dermal irritation potency of MMA appears to be low, as can be concluded from a number of studies with rabbits, guinea pigs and rats.

The rabbit data on skin and eyes are from Spealman et al. (1945). Symptoms in the eye are inflammation and oedema, returning to normal after 72 hr. On the skin MMA caused fleeting and mild irritation. In all cases 100% MMA was used. The dermal irritation for Freund Complete Adjuvant (FCA) pre-treated guinea pigs was low.

The maximum non-irritating concentration was undiluted MMA (Van der Walle et al. 1982). Some indirect evidence for a low dermal irritation potency for guinea pigs can be derived from the high concentrations used in sensitisation tests. The concentrations used ranged from 50% (in 70% ethanol) (Gad et al. 1986) to 100% (Gad 1988).

Finally, some indication for low dermal irritation for rats is found in a study which was primarily aimed as a dermal absorption experiment (see Section 5.1). Three hours of occlusive exposure of 100% MMA daily for 8 weeks caused keratolysis without ulcerations in rat tail (Verkkala et al. 1983, Kanerva and Verkkala 1986).

A polymerising MMA product, rubbed in daily for 2 min during four weeks on the backs of 14 rabbits induced erythema (2 animals), erosions (3 animals); ulcerations (5 animals), crusts (7 animals) and desquamation (3 animals). It is not clear whether the compound was removed after the rubbing-in. Although the

process of polymerisation is exothermic, this does not cause the irritant effects. A less severe testing scheme induced less irritant effects in intensity and extent. However, a possible allergic component could not be excluded (Spiechowicz 1971).

Sensitisation

Gad (1988) induced sensitisation in guinea pigs using the Guinea Pig Maximisation Test (GPMT). The incidence was 30% when 100% MMA was used for induction and 5% for challenge. The GPMT was also used by Van der Walle et al. (1982). For induction either 0.5 M (= ca. 6% w/w) and 1 M or 0.5 M and 100% MMA were used. Challenge was with 100% MMA. The incidence of sensitisation was respectively 20 and 30%. The test with FCA yielded a sensitisation percentage of 25%. Two other studies failed to induce sensitisation in guinea pigs (Parker and Turk 1983 and Marzulli and Maguire 1982). Five different immunisation methods were used, among them the GPMT. In all cases zero animals were sensitised, probably because of low dosages (ranging from 0.2 to 10%).

Sensitisation in mice was induced with a new type of test when using 50% MMA for induction and challenge. The incidence was 44%. This test, the Mouse Ear Swelling Test (MEST), compares the thickness of the treated ear with the untreated ear (Gad et al. 1986). Dunn et al. (1990) evaluated the MEST again; they found that none of the 14 mice responded when 50% MMA was used both for induction and challenge. The same strain of mice was used as by Gad et al. (1986) and two laboratories with prior MEST experience performed the experiments. Dunn et al. (1990) considered their own outcome false negative and concluded that the MEST is not reliable for detecting weak to moderate contact allergens.

No sensitisation was observed in the rat, in a study on dermal absorption (Kanerva and Verkkala 1986).

Chung and Giles (1977) found that challenge with MMA dissolved in 95% ethanol in guinea pigs did not induce skin reactions because of the rapid evaporation from the skin surface. Immunisation by the intradermal (id) route or by the id plus topical routes had very weak or negligible skin reactions after id challenge with MMA. However, all animals challenged with methacrylates in olive oil showed strong positive reactions regardless of the route of immunisation, immunogen dose or identity of the monomer. A concentration of 0.4% MMA in olive oil induced skin reactions in 83-95% of the animals (group size 19-25 animals). After immunisation with MMA cross sensitisation was

observed to ethylmethacrylate and butylmethacrylate in 99-100% of the animals. After immunisation with ethylmethacrylate or butylmethacrylate 98-100% of the animals cross-reacted with MMA.

Clemmensen (1984) used the guinea pig maximisation test (GPMT) to study possible cross sensitisation. Guinea pigs immunised with MMA cross-reacted with 100% ethyleneglycoldimethacrylate (3/10 animals), 100% triethylene-glycol-dimethacrylate (4/10 animals), and 100% 2-hydroxyethylmethacrylate (6/10 animals) but not with 100% trimethylolpropanetrimethacrylate, 2% 1,6-hexanedioldiacrylate, 2% pentaerythritoltriacrylate or 2% trimethylolpropanetri-acrylate (0/10 animals in all cases). Guinea pigs immunised with 2-hydroxy-propylmethacrylate, 2-hydroxyethyl-methacrylate, ethyleneglycoldi-methacrylate, triethyleneglycoldimethacrylate or trimethylolpropanetri-methacrylate did not cross-react with 3% MMA (12-20 animals used per study group).

Also in another study, guinea pigs did not cross-react with MMA after immunisation with methylacrylate, methylvinylketone, 4-vinylpyridine, trimetholylpropanetriacrylate or pentaerythritoltriacrylate. Per study group 5 animals were used (Parker et al. 1985). Perhaps the negative outcome can be ascribed to the low concentrations used: the highest concentration was 5%.

5.2.2 *Acute toxicity*

The acute toxicity of MMA is low. Only after iv or ip administration the LD,, was lower than 1000 mg/kg. According to the classification and labelling guidelines of the EC (1983) there is no need to label MMA as a dangerous compound.

In rats and mice death is preceded by hypoactivity, dyspnoea and anaesthesia (NTP 1986). Older data also mention a fall in blood pressure, irregular respiration, lacrimation, defaecation, urination, followed by respiratory failure and cardiac arrest (Autian 1975).

Brain research in the rat indicated that exposure to air concentrations of 1664 ± 83 mg/m^3 for 1 h depressed the electrical activity in several areas of the brain. The authors speculate that this loss of activity can be an explanation for the often heard complaints of loss of appetite by persons occupationally exposed to MMA (Innes and Tansy 1981).

Data on the acute toxicity of MMA are presented in Tables 6 and 7.

Table 6 Oral, intravenous, subcutane, dermal and intraperitoneal toxicity of MMA.

species	parameter	value (mg/kg)	reference
mouse	oral LD 50	5,296	Lawrence et al. 1974
	oral LD 50	5,200	Tanii and Hashimoto 1982
	sc LD 50	5,950	Spealman et al. 1945
	iv LD 50	297	DFG 1984
	ip LD 50	940	Spealman et al. 1945
	ip LD 50	1,120	Lawrence et al. 1972
	ip LD 50	1,130	Lawrence et al. 1974
	ip LD 50	1,133	Revell et al. 1992
rat	oral LD 50	9,440	Spealman et al. 1945
	oral LD 50	7,800	IARC 1979
	oral LD 50	8,000	ACGIH 1986
	oral LD 50	8,500	DFG 1984
	oral LD 50	7,550 - 15,100	Lawrence et al. 1974
	sc LD 50	7,080	Spealman et al. 1945
	sc LD 100	12,300	Borchard 1981
	ip LD 50	1,700	Spealman et al. 1945
	ip LD 50	1,250	Singh et al. 1972
	ip LD 50	2,640	Lawrence et al. 1974
rabbit	oral LD Lo	6,550	IARC 1979
	oral LD 50	6,000	ACGIH 1986
	dermal LD 50	> 7,550	Lawrence et al. 1974
	dermal LD 50	> 9,440	Autian 1975
	dermal LD 50	>10,000	Clayton and Clayton 1981
guinea pig	oral LD 50	5,950	Spealman et al. 1945
	sc LD 50	5,950	Lawrence et al. 1972
	ip LD 50	1,890	Spealman et al. 1945
dog	oral LD 50	4,720	Spealman et al. 1945
	sc LD 50	4,250	Spealman et al. 1945

Vainiotalo et al. (1984) exposed male Wistar rats to thermodegradation products of poIyMMA. The main product was MMA, although many other compounds were also present. They were not identified. The concentration of MMA was 1,000 ± 90 mg/m^3. Groups of rats were exposed 6 h to night once, five or ten times. The lungs and brain were studied for biochemical effects. In the lung the activity of several enzymes decreased, but did not decrease with an increasing number of exposures. In the brain the activity of several enzymes was increased, again, no dose-response relationship was obtained. The concentration glutathione in lung and brain was decreased. Scanning electron microscopy of the exposed lungs showed disorganisation of ciliated cells, and damage of epithelial serous cells (Clara cells).

Table 7 Toxicity of MMA after acute inhalation.

species	exposure	parameter	effects	reference
mouse	5 h (47700 mg/m³)	9/15 †	depression, liver degeneration, hepatitis and focal necrosis	Spealman et al. 1945
	3 h (96400 mg/m³)	20/20 †	depression, liver degeneration, hepatitis and focal necrosis	
	3 h (61800 mg/m³)	15/15 †	depression, liver degeneration, hepatitis and focal necrosis	
	3 h h (26200 mg/m³)	1/20 †		
	3 h (55000 mg/m³)	LC 50	depression, liver degeneration, hepatitis and focal necrosis	
	13000 mg/m³	LC Lo		Lewis 1992
	56 min (115000 mg/m³) (by blowing)	LT 50		Lawrence et al. 1974
	26.95 min (164000 mg/m³) (by bubbling)	LT 50		Lawrence et al. 1974
	4 h (4955-19269 mg/m³)	all lived (n = 60)		NIP 1986
	4 h (66560 mg/m³)	10/10 †	no compound-related effects (hypoactivity, dyspnoea, anaesthesia) were observed at necropsy	NTP 1986
rat	4 h (4955-19269 mg/m³)	all lived (n = 10)		NTP 1986
	4 h (66560 mg/m³)	9/10 †	no compound-related effects (hypoactivity, dyspnoea, anaesthesia) were observed at necropsy	NTP 1986
	4 h (29500 mg/m³)	LC 50		Tansy et al. 1980a
	2 h (50000 mg/m³)	LC 50		DFG 1984
	8 h (15000 mg/m³)	LC 50		Clayton 1981
	72.2 min (110800 mg/m³)	LT 50		Nicholas et al. 1979
rabbit	4 1/2 h (17500 mg/m³)	LC Lo		Clayton 1981
guinea pig	4 1/2 h (72100 mg/m³)	6/6 †	CNS depression, liver degeneration	Spealman et al. 1945
	5 h (19000 mg/m³)	LC Lo	Liver degeneration and focal necrosis	DFG 1984
dog	3 h (41200 mg/m³)	2/2 †	CNS Depression; excessive salivation, irritation, liver degeneration and tubular degeneration in kidney	Spealman et al. 1945
	1 1/2 h (72100mg/m³)	2/2 †		Lawrence et al. 1974
	26.95 min (164000 mg/m³) (by bubbling)	LT 50		Lawrence et al. 1974

4 h (4955-19269 mg/m³)	all lived (n = 60)		NTP 1986
4 h (66560 mg/m³)	10/10 †	No compound-related effects (hypoactivity, dyspnoea, anaesthesia) were observed at necropsy	NTP 1986

Additional data in SCOEL document

Nasal lesions (characterized by degeneration or atrophy specifically in the olfactory region of the nasal epithelium) were observed in rats acutely exposed to 200 ppm for 6 hours (Mainwaring et al. 2001)SCOEL4.

5.2.3 Short-term toxicity

After inhalation exposure to MMA local effects in the nose, respiratory tract and fur and systemic effects on lung, liver, kidney and gastrointestinal tract have been observed. After oral administration of high dosages behavioural changes have been observed.

Inhalatory exposure

MMA can exert local effects in the nose and respiratory tract (mice and rats). A remarkable feature is that an effect on fur (rats) is reported. No explanation is given, but it must be poor grooming activity. MMA can exert systemic effects like dyspnoea, liver and kidney degeneration and a reduction in gastrointestinal activity (several animal species).

Local effects

Redness and swelling of the nasal region was found in mice when exposed to 20,800 mg/m³, 6 h per day with 10 exposures in 11 days. Nasal effects do not occur in rats with the same exposure regimen or in mice at lower concentrations. With three months exposure MMA induced nasal effects in rats. From 12,480 mg/m³ and higher for males and from 8,320 mg/m³ and higher for females, with intermittent exposure, inflammation associated with necrosis and loss of olfactory epithelium occurred in the nasal cavity. After three months of exposure all mice had metaplasia of the nasal epithelium even at the lowest concentration tested: 2,080 mg/m³ (500 ppm) (NTP 1986).

Longer exposure regimens induced damage in the tracheal mucosa. Cilia and microvilli were absent in rats when exposed to 482 mg/m^3 (116 ppm), 7 h per day, 5 d per week for 6 months (Tansy et al. 1980c).

Lung fibrosis and oedema were found in rats exposed to 4,160 mg/m^3, 8 h per day for 7 days (Tansy et al. 1980c). The fibrosis is a remarkable observation since this usually develops only slowly. It is therefore doubtful whether the diagnosis was correct. Moreover, the fibrotic changes in the lung occurred in control animals to a lesser degree, casting further doubt on the possible toxicological importance of this change.

Systemic effects

The main systemic effects found are dyspnoea, liver and kidney degeneration, fibrosis and oedema in the lung and a decrease in gastrointestinal motility.

Mice had difficulty breathing when exposed to 20,800 mg/m^3, 6 h per day with 10 exposures in 11 days (NTP 1986).

Liver degeneration, described as swollen cells with altered nuclei, was found in guinea pigs, when exposed to 65,500 mg/m^3, 3 h per day for 3 days (Spealman et al. 1945). Liver and kidney degeneration was found in dogs when exposed to 46,800 mg/rn3 either 0,5 h per day for 15 days or 1.5 h per day for 8 days (Spealman et al. 1945). The lowest concentration inducing possible liver damage in rats was 482 mg/m^3, when exposed for 7 h per day, 5 d per week for 3 months. However, these changes were apparently unrelated to dose or time (Tansy et al. 1980b).

Changes in blood chemistry were within the range of normal variation in rats when exposed either to a high concentration for a short period (4,160 mg/m^3, 8 h per day for 7 days, Tansy et al. 1980c) or to a lower concentration for a longer period (482 mg/m^3, 7 h per day, 5 d per week for 3 months, Tansy et al. 1980b).

No systemic effects were observed in male and female rats, when exposed intermittently for 3 months to 4,160 mg/m^3 and 2,080 mg/m^3, respectively. At 4,160 mg/m^3 and higher female rats showed a dose-related increase in brain lesions (malacia (softening) and gliosis (hyperplasia of the neuroganglia)). Neither male nor female mice showed any systemic effects when exposed to 4,160 mg/m^3, with the same dosing regimen. At 8,320 mg/m^3 and higher male mice showed a dose-related increase in renal lesions (cortical necrosis, cortical tubular degeneration and/or focal mineralisation). Also the liver showed necrosis (NTP 1986).

A reduction in gastrointestinal activity was observed in some studies in rats and dogs. This activity consists mainly of retrograde peristalsis and segmental

contractions and therefore a decrease results most of the time in an increase in faecal production. The effects noted are immediate, and reversible upon removal of the agent. Exposure to MMA concentrations of 480 mg/m^3, 7 h per day, 5 d per week for 3 months decreased the small intestinal transit performance, as was measured by quantifying faecal production. However, only in weeks 7, 10 and 11 faecal excretion was significantly increased compared to the control rats. Faecal production was normal during the days without exposure (Tansy et al. 1980b). Exposure to 483 mg/m^3 (116 ppm) 8 h per day, 5 d per week for 6 months was associated with a significant decrease in intestinal transit performance in rats. These rats had also significantly lower adiposity, as measured by the popliteal fat pad, than those of a similar group which have received sham exposures (Tansy et al. 1976).

On the other hand, the NTP study (1986) did not mention anomalous intestinal activity, exposing rats and mice for 1, 10 or 11 days, 3 months or 2 years.

For more information on the influence of MMA on contraction see Section 7.2.7.

Oral administration

Administration by gavage of MMA did not significantly increase the incidence of forestomach mucosal cell proliferation and hyperkeratosis in rats when MMA was administered at 100 and 200 mg/kg, 5 d per week for 2 weeks to groups of 8 male F344 rats (Ghanayem et al. 1986).

Behavioural changes were observed when rats received 500 mg/kg by gavage daily for 21 days. Adult male Wistar rats showed impaired locomotor activity and increased aggressiveness. Analysis of a separate batch of rats indicated an increase in biogenic amines in several parts of the brain. The level of biogenic amines may be related to the behavioural changes observed. Unpublished data indicate that no effect on behaviour was observed at dosages of 100 and 200 mg/kg (Husain et al. 1985).

5.2.4 Long-term toxicity and carcinogenicity

No evidence for carcinogenicity has been found in the animal species studied so far, after inhalatory or oral administration.

Inhalation exposure

There is no evidence that inhalation exposure of MMA causes an increase in neoplasms in rats, mice, Syrian Golden hamsters or dogs. Two studies have been reported. One (Smith et al. 1979) communicates in abstract form the negative findings in rats, hamsters and Beagle dogs. Male and female Fischer 344 rats and Syrian Golden hamsters were exposed to 0, 104, 416 or 1664 mg/m^3, 6 h per day, 5 d per week for 24 and 18 months, and male beagle dogs were exposed to 0, 416 or 1664 mg/m^3 MMA, 6 h per day, 5 d per week for 3 months. Gross and histopathologic evaluations were made after exposures of 3 months to dogs, 18 months to hamsters and 3, 12 and 24 months to rats. With the exception of mild rhinitis in rats, no exposure-related effects were observed.

Many years later (in 1993?) the histopathology of the rat nasal tissues was reviewed. New sections were made, including sections deeper into the tissue blocks, ensuring that the olfactory region was consistently sectioned. The review changed the original interpretation in two key areas. Firstly, the original diagnosis of inflammatory polyps in the nasal cavities of three rats (one at 416 mg/m^3 and two at 1664 mg/m^3) was changed in line with contemporary classification to adenomas. Moreover, the review resulted in two polypoid adenomas (one at 416 mg/m^3 and one at 1664 mg/m^3) instead of three. Secondly, treatment-related irritant effects were distinguished from nonspecific, background inflammatory irritation. The extensive sectioning of the olfactory region revealed that, indeed, the olfactory epithelium was the target tissue in rats exposed to MMA concentrations of 416 and 1664 mg/m^3, with the effects observed at 416 mg/m^3 being only slight and in a fraction of the animals. The nasal cavities of rats exposed to 104 mg/m^3 were morphologically similar to those of control animals. This new interpretation enabled the NAEL for nasal lesions to be established at 104 mg/m^3 (Röhm 1993).

The second study was carried out within the framework of the National Toxicology Program. and a detailed report has been prepared (NTP 1986). Groups of 50 male F344/N rats and 50 B6C3F$_1$ mice of both sexes were exposed to 0, 2080 or 4160 mg/m^3, 6 h per day, 5 d per week for 102 weeks. Groups of 50 female F344/N rats were exposed to 0, 1040 and 2080 mg/m^3 on the same schedule. Survival rates of the treated animals were similar to those of their respective controls. After several weeks of study body weights were reduced (up to 19% reduction compared to control), but returned to normal from week 89 onward. Upon necropsy an extensive histopathological examination was

performed on all animals. No compound-related neoplastic lesions were found in treated mice or rats. An increased incidence of mononuclear cell leukaemia in high dose female rats was not significant. Treatment-related effects were found in the nasal region: inflammation of the nasal cavity and degeneration of the olfactory epithelium in mice and rats; in mice, epithelial hyperplasia of the nasal cavity was also observed. The lesions are described in more detail by Chan et al. (1988). No other effects were seen.

Additional data in SCOEL document

In a two-year inhalation study in rats, a clear NOAEL was evident at 25 ppm (Röhm and Haas, 1979; Lomax, 1992).[SCOEL11, SCOEL12] At 100 ppm there were "minimal to slight" changes in the nasal olfactory epithelium (epithelial cell degeneration/atrophy and replacement of damaged cells with ciliated cells, basal cell hyperplasia, and olfactory mucosa/submucosa inflammation); and at 400 ppm these changes were somewhat more pronounced in the olfactory region, and also evident in the respiratory region of the nasal epithelium.

Oral administration

No evidence for carcinogenic activity of MMA was found in rats and dogs after oral dosing for two years. Only one study is available (Borzelleca et al. 1964). Groups of 25 male and female Wistar rats received 0, 6, 60 and 2000 ppm (ml/l) MMA in their drinking water 7 d per week. At the start of the fifth month the low and medium levels were raised to 7 and 70 ppm, respectively. These levels in drinking water were calculated as equivalent to a dietary intake of ca. 14.3, 137 and 3360 ppm (mg/kg) in the food for females and 12.2, 115 and 3,210 ppm (mg/kg) in the food for males. Groups of 2 male and 2 female Beagle dogs received daily by gavage 0, 10, 100 and 1,000 ppm MMA, calculated as dietary equivalent. The high dose was increased to 1,200 ppm at 5 weeks, to 1,400 ppm at 7 weeks and to 1,500 ppm at 9 weeks and for the rest of the study. After two years both rats and dogs were sacrificed. In rats and dogs mortality, organ-to-body-weight ratio, haematologic values and urine concentrations of protein were within normal limits for all groups. Two exceptions: the elevated relative kidney weight in high dose female rats is not further explained and the lower relative spleen weight in middle dose dogs were not considered of biological significance. Extensive histopathology showed no treatment-related abnormalities or lesions in neither rats nor dogs.

The negative findings in the dogs after oral and inhalatory exposure are equivocal because the dosing of dogs was not lifetime, neither was the moment of observation at the end of the dog's life.

Conclusion

The Committee concludes that under the conditions of the 2-year inhalation studies by NTP, there is no evidence of carcinogenicity of MMA for male F344/N rats exposed at 2080 or 4,160 mg/m^3, for female F344/N rats exposed at 1,040 or 2,080 mg/m^3, and for male and female B6C3F$_1$ mice exposed at 2,080 or 4,160 mg/m^3. The only treatment related effects found were lesions in the nose, which were still present at the lowest concentration tested (1040 mg/m^3, intermittent exposure) in female rats.

Furthermore, there is no evidence of carcinogenicity of MMA for Syrian Golden hamsters, inhaling 104, 416 or 1,664 mg/m^3 for 18 months. There is no evidence of carcinogenicity of MMA for Wistar rats after dosing 6, 60 and 2,000 ppm in drinking water for two years.

5.2.5 *Mutagenicity*

MMA is not mutagenic for bacteria. In high dosages, MMA induces clastogenic effects and SCEs in mammalian cells in vitro both with and without metabolic activation and in occupationally exposed workers with peak exposures. The data are summarised in Table 8.

Several brands of polyMMA, containing MMA and several other compounds, were negative in the Ames test with and without metabolic activation (strains TA98, TA100, TA1535, TA1537). Moreover, the brands did not induce micronuclei in bone marrow of NMRI SPF mice after a single ip injection (Jensen et al. 1991).

The positive results were only obtained at low survival rates (ca. 10%). Moreover, Moore et al. (1988) noted that not all cultures treated with more than 2,000 µg/ml showed a positive response. But the concentrations used in the test are so high, that in reality they do not constitute a hazard.

However, in most, if not all, MMA samples hydroquinone is present as an inhibitor of spontaneous polymerisation. Hydroquinone can induce SCEs in mammalian cells in vitro with and without metabolic activation. Hydroquinone induces chromosomal aberrations only after metabolic activation (Galloway et al. 1987). The quantitative results are presented in Table 9.

If 100 ppm of hydroquinone, which is a relatively large amount, would have been added to MMA, there would be only 0.5 µg/ml hydroquinone in a sample of 5,000 µg/ml MMA. From the study described above it can be concluded that hydroquinone might be the cause of the positive results of the mutagenicity tests with MMA. On the other hand Moore et al. (1988) stated that NTP found a concentration of 0.62 µg/ml of hydroquinone to be negative in the SCE and chromosomal aberration test. Additional tests have to be performed to exclude possible mutagenicity by hydroquinone.

However, in view of the negative findings in the carcinogenicity studies the genotoxic activity of MMA may be less relevant.

Table 8 Mutagenic and genotoxic data..

type of test	species	conc. tested	remarks	results	reference
Ames	Salm. typh. TA1535, TA1537, TA1538, TA98, TA100	< 10,000 g/plate		- NA[a]	NTP 1986
Ames	,,	40-10,000 g/ plate	MMA was diluted in DMSO; addition of 2 g hydroquinone or p-methoxyphenol to positive control plate did not influence the response of TA100	- NA - RLUA[b]	Waegemakers and Bensink 1984
Ames	Salm. typh. TA100, TA1535, TA1537, TA98	10-10,000 g/ plate	solvent: DMSO; purity of MMA > 99%	- NA - HLiA[c]	Zeiger et al. 1987
Ames	Salm. typh. TA100, TÁ1535, TA97, TA98	33-6,666 g/plate	solvent: DMSO; purity of MMA> 99%	- NA - HLiA - RLiA	Zeiger et al. 1987
		33-6,666 g/plate	solvent: DMSO; 6,666g/plate was slightly toxic to all species	- NA - HLiA - RLiA	NTP 1986
Ames	Salm. typh. TA1535, TA1537, TA1538, TA98, TA 100	0.15 - 4.7 mg/ plate		- NA - RLiA	Hacmiya et al. 1982
mutation	L5178Y TK +/- mouse lymphoma	118-944 g/ml	4 h treatment	+ NA + RLiA	NTP 1986
clastogenic	L5178Y TK +/- mouse lymphoma	1,000-3,100 g/ ml	4 h treatment; solvent DMSO; 10 ppm methylhydroquinone was added; small colony formation, TFT resistant mutants, gross aberrations, 2000 g/ml induced a positive response	+ NA	Moore et al. 1988
		250-1,000 g/ml	solvent DMSO	+ RL1A	earfield et al 1991
clastogenic	Chinese hamster ovary cells	750-3,000 g/ml 16-1,600 g/ml	there was a slight dose-related increase in chromosomal aberrations	+ NA + NA	NTP 1986 Anderson et al. 1990

clastogenic	Chinese hamster ovary cells	160-5,000 g/ml	increase of frequency of aberrations only at the highest, near-lethal dose	+ RLiA	NTP 1986
induction of micronuclei	mouse	1.13 - 4.52 mg/ kg single oral dose	test on bone marrow	-	Hacmiya et al. 1982
		1.13 mg/kg four oral doses		-	
induction of SCEs	Chinese hamster ovary cells	50-1500 g/ml 5-1250 g/ml 50-5000 g/ml	there was a dose-related increase in one test a weak pos. response	+ NA + NA + RLiA	NTP 1986 Anderson et al. 1990
induction of SCEs	occupationally exposed	77-90 mg/m^3 TWA 8 h with peak expos. to 700-1700 mg/ m^3; 3-90 mg/m^3 TWA 8 h	test in peripheral lymphocytes; the control group consisted of 31 healthy male workers	+	Marez et al. 1991
				-	
dominant lethal test	20 male CD-1 mice	416, 4160 or 3744 mg/m^3 6 hr/day for 5 days	mating with females; no effect on fertility, pre-implantation egg-loss or early or late post-implantation foetal death	-	ECETOC 1994

[a] NA = not activated
[b] RLiA = rat liver activated
[c] HLiA = hamster liver activated

Table 9 Mutagenic data for hydroquinone tested in Chinese hamster ovary cells (Galloway et al. 1987).

	conc. tested	results	LEC[a] (g/ml)
SCE NA	0.5-5 g/ml	+ NA	< 0.5[b]
RLI	50-800 g/ml	+/+[c] RLiA	50/600[c]
ABS NA	5-20 g/ml	- NA	20
RLI	150-600 g/ml	+ RLiA	450

[a] Least effective concentration tested (LEC) is the lowest dose to give a statistically significant increase ($p < 0.05$) in aberrations or a 20% increase in SCEs.
[b] Lowest dose tested gave a positive response.
[c] Individual trial results (separated by "/").
ABS = aberrations.

5.2.6 *Reproduction toxicity*

Effects on fertility

According to Health Council 1994 and SCOEL 2005, there were no fertility studies on MMA available at the time.

Additional information*

Male Sprague-Dawley rats were exposed to MMA drinking water during eight months. Concentration levels were 0, 4, 8, 16 and 32‰ (v/v)**. At sacrifice after eight months, there was no effect on average food and water consumption or on average body weight gain. Compared to pre-exposure levels of serum testosterone, the rats exposed to 32‰ (n=10) showed a decrease of 71.7% ($p = 0.002$). After eight months, in the highest exposure group, serum testosterone levels were increased in two of the ten animals. Body weight gain in these animals after 8 months (38%) was higher than in the remaining animals (23%). Histological examination of testis, epididymis, vas deferens and seminal vesicles revealed no abnormalities in testis, epididymis and vas deferens, whereas partial atrophy of the epithelium of seminal vesicles was observed in 7/10 males of the high exposure group.[7,8]

Effects on development

MMA can cause foetotoxicity in rats characterised by decreased foetal body weights and crown-rump length, by delayed ossification, and by the occurrence of haemangiomas after inhalation or ip exposures (four studies). In mice no effects have been found at the dosing regimens used (two studies).

Inhalation studies in rats were performed by Nicholas et al. (1979), Luo et al. (1986), DFG (1984) and Solomon et al. (1991 and 1993).

Nicholas et al. exposed groups of 22-27 pregnant Sprague Dawley rats to 112,000 mg/m^3 for 17.2 min or for 54.2 min per day on gestation day (GD) 6-15. The dosing induced an initial decrease in maternal food consumption and body weight. Both treated groups had a decreased foetal body weight and foetal crown-rump length, and delayed ossification of the sternebrae. The long exposure group had haematomas and delayed ossification of the vertebrae. No difference was found between the treated and control animals in the number of corpora lutea per dam, implantations per litter, live foetuses per litter and the percentage resorptions and early foetal deaths.

Luo et al. (1986) exposed groups of pregnant rats to 520 or 4480 mg/m^3 for 2 h once every three days on GD 6 - 18. No maternal toxicity was observed. In

* Data retrieved up to October 2011 and not mentioned in any of the two advisory reports.
** Assuming methyl methacrylate was administered in the drinking water, these concentrations correspond to intakes of approximately 0, 375, 750, 1,500 and 3,000 mg/kg bw/day.

both groups delayed ossification occurred; in the high concentration exposure group an increase in resorptions was observed. No further data are available.

DFG (1984) describe a study in which groups of pregnant rats were exposed to MMA concentrations of 104, 416 or 4,160 mg/m^3, 5 h per day on GD 6-15. The highest concentration level increased the number of resorptions. No effects were found on embryos or foetuses at the middle dose. Unfortunately the original study was not made available by the company. Therefore it is not possible to judge the data in detail.

Solomon et al. (1991 and 1993) exposed groups of 22 - 25 pregnant (Crl:CD^{r}BR) rats to concentrations of 0, 412, 1,265, 4,900 or 8,437 mg/m^3, 6 h per day on gestation days GD 6-15. At the two highest dosages a transient decrease in maternal body weight gain was observed ($p < 0.05$ compared to the control group) on GD 8, 10, 13 and (high dose only) GD 16. Treatment-related decreases were noted on feed consumption at all exposure levels. At GD 20 all body weights were significantly similar to those in the control group. No treatment-related changes were detected among dams during the gross post-mortem examination. There were no treatment-related changes in litters produced or in the mean number per litter of corpora lutea, implantations, resorptions, live or dead foetuses or sex ratio. Foetal body weights were similar between the control and treated groups. There were no treatment-related increases in the type or incidence of external, visceral or skeletal malformations, developmental variations, or variations due to retarded development. Therefore, toxicity to the conceptus was not evident, even at exposure levels that resulted in overt maternal toxicity.

One study with *intraperitoneal* exposure in rats is available (Singh et al. 1972). The dosages represented 0.1, 0.2 and 0.33 of the ip LD50. Groups of 5 pregnant Sprague Dawley rats were injected ip with 125, 250 or 418 mg/kg on GD 5, 10 and 15. The two highest dosages increased the number of gross abnormalities (haemangiomas) in the foetuses.

The two studies in mice are from McLaughlin et al. (1978) and Tansy and Kendall (1979). Both use the inhalation route. Exposure to 464 or 1664 mg/m^3, 6 h per day on GD 4-13 did not induce teratogenicity or an increase in resorptions (Tansy and Kendall 1979, dosing regimen is described by DFG 1984). McLaughlin et al. (1978) exposed a group of 18 pregnant ICR mice to 5,530 mg/m^3, 2 times 2 h per day on GD 6-15. No maternal or foetal toxicity was observed. The foetal weight in the treated group was slightly increased compared to control. But this is of doubtful toxicological importance as food consumption

was not recorded and there were no other groups used to establish a possible dose-response.

MMA was tested together with 79 other rubber chemicals in three-day chicken embryos by Korhonen et al. (1983). The compounds were dissolved in either acetone or water and dropped into the air chamber of the egg. MMA was one of the 24 chemicals with an incomplete, irregular or flat dose-response curve for early death. The ED50 for malformed embryos was 22 µmol per egg. Together with sodium nitrite MMA was the least potent compound.

Conclusion

At high inhalation exposure concentrations (112,000 mg/m^3) foetotoxic (not teratogenic) effects were found in rats however, these effects were not found at lower concentrations (4,480 or 520 mg/m^3). An increased number of resorptions was found at 4,480 and 4,160 mg/m^3. However, these data are only available in abstract form. No data are given on the strain used, the number of dams per treatment group, or exactly how many resorptions were found. In a recent study in rats, of which a comprehensive report is available, no foetal effects, nor an increase in resorptions was found at concentrations up to 8,437 mg/m^3.

5.2.7 Other studies

MMA caused a reduction in contractile force of isolated rat and rabbit atria accompanied by an increase in spontaneous rate. The lowest dose tested (3.7 mM = 370 mg/l) caused already an effect. This negative inotropic effect was reversed by elevating bath calcium concentrations; thus, it seems likely that MMA may act by limiting functional access of extracellular calcium to the tissue. Isoproterenol reduced but did not eliminate the effect of MMA on contractile force (Baran et al. 1992).

Revell et al. (1992) gave single acid repeated iv injections of 15, 30, 60 and 90 mg/kg MMA to groups of four New Zealand white rabbits. The injections were given in a stepwise manner sequentially at a minimum of 20 min intervals. The compound caused a transient bradycardia, tachypnoea, raised central venous pressure and arterial hypotension in low doses with rapid recovery, though the effects were sustained at higher cumulative doses of 60 mg/kg and above.

MMA blocked receptor-mediated contraction and the phasic and tonic portions of the KCl-induced contraction of the isolated rat uterus. The lowest dose tested (1 mM = 100 mg/l) caused already an effect. The effects of MMA

could be antagonised by increasing the concentration of calcium. In the Cat^{2+}-free, K^{+}-depolarized preparation, MMA produced a dose related depression of contraction (Born et al. 1988).

A depression on gastric motor function during exposure to MMA was found in rats and one human volunteer. The rats were anaesthetised, MMA vapour was administered by means of a tracheostomy tube or via the room air and pressure changes produced by gastric motor activity were recorded. The volunteer received an open-tip catheter which was inserted via the oral route into the region of the gastric antrum. With this device intragastric pressure activity was recorded. In both cases the concentration of MMA in the air could not be calculated (Tansy et al. 1974).

Also in anaesthetised dogs MMA inhibited gastrointestinal contraction. Twelve adult mongrel dogs of both sexes received during 3 - 12 minutes (a fixed length) air with 8,320 mg/m^3 MMA (2,000 ppm). Motor inhibition always continued for a variable time (ca 10-15 min) subsequent to the cessation of MMA vapour administration. Another series of experiments determined that the administration of blood from a dog receiving MMA vapour produced gastrointestinal motor inhibition in another dog not connected to the experimental gas mixture. Therefore, it is concluded that, aside from any reflex effects produced, MMA vapour in sufficient concentration probably exerts a direct inhibitory effect upon gastrointestinal smooth muscle that is mediated by the cardiopulmonary systems (Tansy et al. 1977).

In normovolemic and hypovolemic dogs the MMA monomer influenced arterial blood pressure, cardiac output and peripheral resistance. A concentration of 2 mg/per 100 percent of bodyweight was infused intravenously and produced vasodilatation of the small blood vessels. The peripheral resistance and blood pressure were decreased in both normovolemic and hypovolemic dogs. The cardiac output was increased in normovolemic, but decreased in hypovolemic dogs (Berman et al. 1974).

Brown and Parmley (1984) did not succeed in inducing a prolongation of atrioventricular conduction intervals in anaesthetised dogs weighing 17-19 kg. The concentration of iv administered MMA ranged from 0.2 to 1 ml as a bolus. This was sufficient to cause minimal to profound haemodynamic changes: increased heart rate and central venous pressure, decreased arterial pressure and systemic vascular resistance.

MMA, given by infusion to anaesthetised dogs caused a sustained hypotension, bradycardia, reduction of cardiac output and stroke volume and increased peripheral resistance. The bolus dose was 31.2 mg/kg. Epinephrine iv could reverse the hypotension but not the bradycardia; isoproterenol iv could

reverse the bradycardia but not the hypotension. Calcium chloride iv reversed all circulatory changes except bradycardia; a combination of atropine and calcium reversed all cardiovascular changes from MMA (Waters et al. 1992).

Also in sheep MMA produced hypertension and lung vascular permeability. Fairman et al. (1984) administered iv 2 or 12 mg MMA per kg bodyweight to 5 or 12 sheep. After the 12 mg/kg dose there was a marked fall in mean systemic blood pressure within 30 s. The blood pressure returned to normal and then decreased, again becoming significantly lower than baseline at 120 min. Mean pulmonary artery pressure increased at 0.5 min then slowly returned to normal over 1 hr.

Dillingham et al. (1983) studied the haemolytic activity of MMA in fresh oxalated rabbit blood. A concentration-response curve was prepared and from this the concentration effecting 5% and 50% haemolysis was determined. It was 7.16 and 8.85 g/l, respectively.

Böhnke et al. (1985) tested the cytotoxicity of MMA in porcine corneal endothelial cells. PoIyMMA is often used for the implantation of intraocular lenses, however, the presence of a residue of the monomer in the polymeric endproduct cannot be avoided. During the incubation period of six days cell damage ranging from vacuolic degenerative changes to necrosis of the endothelial cell layer was observed in the concentration range from 10^{-8} to 10^{-3}%. From these results it may be concluded that MMA levels above 10^{-8}% are toxic to endothelial cells.

5.3 Summary

Observations in humans

- Irritation and sensitisation
  MMA is irritating to skin, eyes and mucous membranes. It can cause sensitiation, the incidence varies from 2 to 15%.

Additional data

The threshold for eye irritation and for sensory irritation of the respiratory tract to airborne MMA vapour appears to be above 100 ppm.

Despite a small number of asthmatic reactions associated with occupational exposure to MMA reported in the literature, the evidence for respiratory sensitisation from MMA has been considered inconclusive. In the majority of the reported cases asthmatic respiratory responses have been attributed to exposure

to transiently high concentrations of MMA that may have resulted in respiratory irritation in individuals with normal airway responsiveness, or perhaps in some cases with pre-existing, generally hyperreactive airways.

- Short-/long-term exposure
  MMA induces various effects on the central nervous system. No dose-response relationship can be established.
  After dermal absorption MMA reportedly may reduce nerve conduction velocity and may cause coldness and numbness.

- Epidemiological studies
  Effects on the central nervous system, irritation of eyes and upper respiratory tract and changes in several blood parameters are reported without a dose-response relationship.
  No excess was reported in all-cause or cause-specific mortality after exposure to low MMA levels. Only with exposure to high levels of MMA in combination with high levels of ethylacrylate and by-products of a polymerisation process was an increase in colon cancer reported.
  Occupational exposure for at least five years to a mean of 77 or 90 mg/m^3 can induce chronic cough and probably cardiac arrhythmia.

Additional data

In a recent critical review of the epidemiological literature on potential cancer risks from MMA, focusing on cast acrylic sheet manufacturing workers, it was concluded that there is insufficient evidence that MMA is a human carcinogen, based on the lack of consistency of the various studies, the absence of dose-response relationships and the lack of support from studies in animals.

Animal data

- Irritation and sensitisation
  MMA is mildly irritating to the skin of rabbit, rat and guinea pig and to the rabbit eye. MMA may cause sensitisation in mice and guinea pigs. No sensitisation was observed in rats.

Additional data

SCOEL (2005) and ESR (2002) concluded that MMA has a moderate to strong sensitising potential in experimental animals**.**

- Acute toxicity
  The acute toxicity of MMA is low. After a single oral dose the LD50 is higher than 5,000 mg/kg in mice, rats, rabbits and guinea pigs. The inhalatory LC50 for rats is 29,500 mg/m^3 (4 h of exposure) and for mice even higher.

Additional data

In a study referenced by SCOEL (2005), degeneration and atrophy in the olfactory region of the nasal epithelium were observed in rats after 6 hours exposure to 200 ppm MMA.

- Short-term exposure
  - Inhalation exposure, local effects
    The lowest concentration tested in rats, 482 mg/m^3 (= 116 ppm), 7 hr/day, 5 d/week for 6 months induced damage to the tracheal mucosa. The lowest concentration tested in mice, 2,080 mg/m^3 (= 500 ppm), 6 hr/day, 5 d/week for 3 months, induced metaplasia of the nasal epithelium. The ruffled fur (unkempt appearance) found in rats was considered treatment-related.
  - Inhalation exposure, systemic effects
    The lowest concentration tested in rats, 482 mg/m^3 (= 116 ppm), 7 hr/day, 5 d/week for 6 months induced a decrease in small intestinal performance. At high concentrations (20,800 mg/m^3 = 5,000 ppm) for short periods of time dyspnoea was observed in mice.
    Lower concentrations for longer and repeated exposures induced liver and kidney degeneration in guinea pigs, dogs, mice and rats and brain lesions in the rat. No systemic effects were found in male rats and male and female mice exposed for three months to 4,160 mg/m^3 (= 1000 ppm), 6 hr/day, 5 d/week. In female rats no systemic effects were observed at 2,080 mg/m^3 (= 500 ppm), 6 hr/day, 5 d/week for 3 months.
  - Oral exposure, local effects
    No cell proliferation was observed in the forestomach of rats after administration of 200 mg/kg, 5 d/week for 2 weeks.

- Oral exposure, systemic effects
  Behavioural changes were observed in rats after administration of 500 mg/kg/day for 21 days. At 200 mg/kg/day behavioural changes were not observed.

- Long-term toxicity and carcinogenicity
  No evidence for carcinogenicity of MMA was found after inhalation exposure in rats, mice, Syrian golden hamsters and dogs.
  After oral exposure there was no evidence for carcinogenicity of MMA in rats and dogs.
  Inhalatory exposure induced nasal lesions in the female rat. In one study at the lowest dose tested (1,040 mg/m^3 (= 250 ppm), 6 hr/day, 5 d/week for 102 weeks) this effect was seen. At this dosage no other treatment-related effects were found. In another study the lowest dose tested (104 mg/m^3 = 25 ppm, 6 hr/day, 5 d/week for 24 months) was a NOAEL.

- Genotoxicity
  MMA is not mutagenic in bacteria. In high dosages MMA induces clastogenic effects and SCEs in mammalian cells in vitro both with and without metabolic activation and in occupationally exposed workers with peak exposures. The genotoxic activity and subsequent contribution of the inhibitor hydroquinone remains to be established.

- Reproductive toxicity

Effects on fertility

Additional data

In a recent study in which male rats were exposed to MMA in water for 8 months, increased serum testosterone levels and partial atrophy of the epithelium of seminal vesicles were observed at concentrations in the water of 32‰ (equivalent to 3,000 mg/kg bw/day).

Effects on development

With respect to *effects on development*, after high inhalation exposure concentrations (112,000 mg/m^3) or ip dosing MMA can induce foetotoxic effects in rats. At lower concentrations (up to 8,437 mg/m^3) with an intermittent dosing

regimen no embryotoxic, foetotoxic or teratogenic effects are found. In mice no reproductive effects have been found at inhalation concentrations up to 5,530 mg/m^3.

- Other studies
  MMA can cause a reduction in contractile force in several muscles in vitro (rat and rabbit atria, rat uterus) and in vivo (rat, dog and human gastric motor activity). MMA exerts effects on cardiac output, blood pressure and vascular changes in rabbits and in anaesthetised dogs and sheep.

Chapter 6

Existing Guidelines, standards and evaluations*

6.1 General population

No information available.

6.2 Working population

Below are shown the occupational exposure limits, which are presently valid (in the year 2011).

Country	Occupational exposure limit (mg/m^3)		Notation
	8-h TWA	15-min TWA (STEL)	
The Netherlands	205	410	
European Commission (SCOEL)	205	410	-
Germany (DFG)	210	410 (excursion factor 2 on 8-h TWA)	Sh (skin sensitizer), C (there is no reason to fear damage to the embryo or foetus when MAK and BAT values are observed)
Great Britain (HSE)	208	416	-

* Text cited from the advisory report by the Health Council published in 1994 (1994/09). Additional data from the SCOEL document and other published data are presented in italic.

Nordic countries:			
Denmark	102	-	H (skin)
Finland	42	210	-
Norway	100	-	H (skin), K
Sweden	200	600	H (skin), S (sensitizing)
The USA:			
ACGIH	205	410	SEN (sensitizing)
NIOSH	410	-	-
OSHA	410	-	-

The Working group of the IARC (1987) concluded that MMA is not classifiable as to its carcinogenicity to humans (group 3), based on data in IARC monograph volume 19 (1979). There was no adequate evidence for human and animal carcinogenicity.

A TLV of 100 ppm (410 mg/m^3) TWA was recommended by the ACGIH (1986) to protect workers against discomfort from irritation and against acute systemic effects based upon data available at that time. However, protection under conditions of long-term exposure is not certain at this TLV, because no information about effects of long-term exposure was available. Elimination of the STEL was recommended until additional toxicological data and industrial hygiene experience become available. References were from 1983 or earlier.

The DFG (1988) lowered the MAK-value from 410 mg/m^3 (100 ppm) to 210 mg/m^3 (50 ppm). They also recommended a maximum peak value of 2*MAK with a maximum duration of 5 minutes for a frequency per shift of eight. The DFG stated that MMA causes a higher than normal number of allergic reactions and that there is no reason to fear risk of damage to the developing embryo or foetus when MAK values are adhered to.

The reason for lowering the MAK value is not clear; it is not based on the 2 years study of NTP (1986).

The establishment of a maximum peak value is based on local irritation.

NTP (1986) concluded that there is no evidence of carcinogenicity of MMA for rats and mice, under the conditions of the two-year inhalation studies-performed.

The Technical and Medical Services of the INRS (Institut National de Recherche et de Sécurité) of France prepared a toxicological data sheet on MMA (INRS 1993). After a summary of the relevant toxicological data the MAC TWA is set at 410 mg/m^3 (100 ppm) and the limit value at 820 mg/m^3 (200 ppm) without any

risk assessment. Regulations are given concerning transport and recommendations concerning storage and medical examination.

ECETOC (1994) reviewed extensively the literature on MMA. The critical effect was considered to be located in the upper respiratory tract of laboratory animals and consists of rhinitis, serous and suppurative inflammation, epithelial hyperplasia and degeneration of the olfactory epithelium. It is expected that humans are less sensitive to this effect, due to species differences. The neurotoxic/central nervous system effects found in occupationally exposed humans are considered to be nonspecific and do not represent neurotoxicity.

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