FOREWORD INTRODUCTION

2,4-PENTANEDIONE

CAS N°:123-54-6

SIDS Initial Assessment Report

For

SIAM 13

Bern, Switzerland, November 2001

1. Chemical Name: 2,4-Pentanedione

2. CAS Number: 123-54-6

3. Sponsor Country: Germany
Contact Point:
BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit)
Prof. Dr. Ulrich Schlottmann
Postfach 12 06 29
D- 53048 Bonn-Bad Godesberg

4. Shared Partnership with:

5. Roles/Responsibilities of the Partners:

- Name of industry sponsor /consortium: Wacker Chemie GmbH, Germany
Contact person:
Dr. Frank Engel
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Johannes_Hess-Str. 24
D-84489 Burghausen
- Process used: see next page

6. Sponsorship History

- How was the chemical or category brought into the OECD HPV Chemicals Progran?: by ICCA-Initiative

7. Review Process Prior to the SIAM: last literature search (update):
27. October 2000 (Human Health): databases medline, toxline; search profile CAS-No. and special search terms
27. October 2000 (Ecotoxicology): databases CA, biosis; search profile CAS-No. and special search terms

8. Quality check process: As basis for the SIDS-Dossier the IUCLID was used. All data have been checked and validated by BUA.

9. Date of Submission: 14 September 2001

10. Comments:

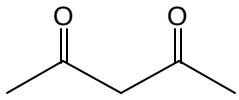
OECD/ICCA - The BUA[1] Peer Review Process

Qualified BUA personnel (toxicologists, ecotoxicologists) perform a quality control on the full SIDS dossier submitted by industry. This quality control process follows internal BUA guidelines/instructions for the OECD/ICCA peer review process and includes:

- A full (or update) literature search to verify completeness of data provided by industry in the IUCLID/HEDSET;
- Review of data and assessment of the quality of data;
- Review of data evaluation;
- Check of adequacy of selection process for key studies for OECD endpoints, and, where relevant, for non-OECD endpoints by checking original reports/publications;
- Review of key study description according robust summaries requirements; completeness and correctness is checked against original reports/publications (if original reports are missing: reliability (4) not assignable);
- Review o f validity of structure-activity relationships;
- Review of full SIDS dossier (including SIAR, SIAP and proposal for conclusion and recommendation for further work);
- In case of data gaps, review of testing plan or rationale for not testing.

[1] BUA (GDCh-Beratergremium fuer Altstoffe): Advisory Committee on Existing Chemicals of the Association of German Chemists (GDCh)

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	123-54-6
Chemical Name	2,4-pentanedione
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

In acute toxicity studies the material proved to be moderately toxic after administration by the oral, dermal and inhalation route, respectively:

LD50 (oral, rat) = 570/760 mg/kg bw (f/m)
LC50 (inhalation, rat) = 5.1 mg/l/4 h (1224 ppm)
LD50 (dermal, rabbit) = 790/1,370 mg/kg bw (f/m)

The values obtained show that 2,4-pentanedione has to be regarded harmful by inhalation, in contact with skin and if swallowed. Also, animal studies on the primary irritancy of the substance demonstrated a low, if any irritation potential both to the skin and eyes after single exposure not leading to a classification as a skin and/or eye irritant. After repeated dermal application to rabbits local skin effects have been observed. Human data give a hint to a local irritating effect. Based on the poor data available the sensitising potential of 2,4-pentanedione cannot be evaluated.

In a 14 week repeated dose inhalation toxicity study in rats 2,4-pentanedione exerted substance related effects on hematological parameters, clinical and urinary chemistry at doses of 300 and 650 ppm (1,217 and 2,711 mg/m^3), respectively. On histopathology, no substance related gross lesions were detectable in the organs examined in all dose groups with the exception of different regions in the brain where hemorrhage and neuronal degeneration was observable at a dose of 650 ppm. In this study no pathological findings were made in the reproductive organs of animals of both sexes, especially in the testes of males. Based on reversible hematological, clinical as well as urinary chemical effects in the 300 ppm group and the histopathological findings in the brains and thymus in the 650 ppm group the NOAEL and LOAEL of this study is defined to be 100 ppm (417 mg/m^3) and 650 ppm (2711 mg/m^3), respectively. These doses can be converted to a NOAEL of 144.1 mg/kg bw/d and a LOAEL of 936.7 mg/kg bw/d assuming a respiratory minute volume of 0.24 l/min and an average weight of 250 g/rat. After repeated treatment of rabbits dermally, effects on thymus, spleen and lymph nodes, hemorrhage and neuronal degeneration in several sections of the brain were seen. After administration by the oral route substance related systemic effects were evident in thymus, liver, lungs, kidneys, bladder and lymph nodes.

No mutagenic effects were seen in the Ames test (except slightly mutagenic effect in the *Salmonella typhimurium* strain TA104) and in the HPRT-assay. A positive clastogenic effect in CHO cells was observed in the absence of metabolic activation. All *in vivo* genotoxicity studies conducted in rats and mice by inhalation did neither increase the number of structural or numerical aberrations nor the number of micronuclei. In contrast 2,4-pentanedione was shown to produce statistically significant increases in the incidence of micronucleated PCEs in mice but not in rats after i.p. administration. Concerning effects on germ cells a dominant lethal assay showed slight effects on fertility

parameters in the (untreated) pregnant females mated with substance treated males being exposed via the inhalation pathway, which are regarded as a consequence of an unusual low control value. In an *in vivo* mouse spermatogonia assay 2,4-pentanedione did not produce chromosomal aberrations after oral administration to male mice at a dose close to the MTD. Overall 2,4-pentanedione shows a direct clastogenic potential *in vitro* which is not expressed *in vivo* by the inhalational route.

There is no reproductive toxicity study available, however the investigations of the reproductive organs of a 14-week inhalation study in rats did not show any effects. The reported effects in the dominant lethal tests in rats were evaluated as not induced by the substance. No chromosomal aberrations were observed in spermatogonia of mice. Therefore no further studies are required under the SIDS regarding fertility.

In an inhalation teratogenicity study in female F344 rats the material did not produce teratogenic effects. Fetotoxic effects (reduced fetal weights in male fetuses) were observed at 200 ppm (=834 mg/m^3) without signs of maternal toxicity. In addition, at 400 ppm (= 1,668 mg/m^3) reduced fetal weights in fetuses of both sexes and a consistent pattern of reduced fetal ossification and skeletal variations as well as reduced maternal weight occurs. The NOAEL for maternal toxicity was 200 ppm (=834 mg/m^3 = 288.2 mg/kg bw/d assuming a respiratory minute volume of 0.24 l/min and an average weight of 250g/rat) based on total resorption of litters in two dams and significantly reduced body weight gain in the 400 ppm group only. The NOAEL for developmental toxicity was determined to be 50 ppm (= 209 mg/m^3 = 72.2 mg/kg bw/d assuming a respiratory minute volume of 0.24 l/min and an average weight of 250 g/rat).

Environment

Due to both the vapour pressure and moderate volatility from water of 2,4-pentanedione (9.2 hPa at 20°C and 0.555 Pa x m^3/mol) release to and exposure via the atmosphere constitutes only a minor pathway. The material is readily soluble in water (166 g/l) and according to the log P_{OW} determined (measured: 0.34 and 0.40) no potential for bio- and geoaccumulation exists. According to a Mackay I calculation the target compartment is the hydrosphere (≈ 90 %) followed by air (≈ 10 %). In the atmosphere a half-life for hydroxyl-radical mediated photodegradation of 14 days at a hydroxyl radical concentration of $1.5x10^6$ hydroxyl radicals/cm^3 was calculated. In a MITI I test the substance was found to be readily biodegradable.

Based on the results of acute aquatic toxicity testing the substance has to be regarded as harmful to aquatic organisms which is supported by chronic toxicity tests performed in *Daphnia magna*:

LC50 (96 h)	= 60.1 mg/l (*Lepomis macrochirus*)
EC50 (48 h)	= 34.4 mg/l (*Daphnia magna*)
IC50 (24 h)	> 300 mg/l (green algae, mainly *Scenedesmus sp.*)
LOEL (EC16, 14 d)	= 0.50 mg/l (*Daphnia magna*)
TT (EC3, 8 d)	= 2.7 mg/l (*Scenedesmus quadricauda*)

From the LOEL of 0.50 mg/l obtained in a chronic toxicity test conducted in *Daphnia magna* a NOEL of 0.25 mg/l was derived yielding a PNEC of 5µg/l applying a safety factor of 50. The test was performed over a period of only 14 days without analytical monitoring of the substance concentration. Therefore as it cannot be excluded that the NOEC from a 21day test with analytical monitoring is lower and the PNEC has to be regarded as tentative. A high acute/chronic ratio was found for *Daphnia magna*. As the substance is known to be a nerve toxin, also for fish a high acute/chronic ratio can be assumed.

Exposure

2,4-Pentanedione is produced by a German and US-American manufacturer. Worldwide production figures for 2,4-pentanedione exceed 1,000 tons/year for each of the producers and is estimated to be 10,000 t/a. The main use is as a chemical intermediate in the production of pharmaceuticals, dyes and plant protection products, respectively. It is also applied in catalyst systems for the polymerisation of olefins and for the control of curing rates in polyurethane coatings. Other uses are found as gasoline and lubricant additives, driers for varnishes and printers inks and colors. The parent compound is also converted to metal-acetoacetonates, which in turn are used as stabilizers in PVC for instance. No information is known regarding procedures applied by industrial customers. Product register information indicates that products may contain the substance in considerable amounts. Product types are e.g. paints and lacquers, cleaning agents and solvents. Among the products there are several for private use.

NATURE OF FURTHER WORK RECOMMENDED

Environment: The substance is a candidate for further work. As for daphnids a high acute/chronic ratio was found and the substance is known to be a nerve toxin, a high acute/chronic ratio is also assumed for fish. From product registers the use of the substance other than intermediate is evident. Therefore, an exposure assessment, and if then indicated an environmental risk assessment should be performed.

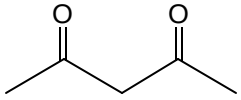
Human Health: The substance is a candidate for further work. In occupational settings where exposure is not controlled and due to information of European product registers exposure to consumers and workers cannot be excluded. As the extent cannot be estimated, a human exposure assessment and, if then indicated, a risk assessment should be performed.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 123-54-6
IUPAC Name: 2,4-Pentanedione
Molecular Formula: $C_5H_8O_2$
Structural Formula:



Molecular Weight: 100.12
Synonyms: acetylacetone; acetyl-propanone-2; 2,4-dioxopentane

1.2 Purity/Impurities/Additives

The purity of the substance exceeds 99 %. Known impurities are water (0.1 %), hexane-2,5-dione (0.1 %), acetic acid (0.05 %) and isopropenyl acetate (0.03 %).

1.3 Physico-Chemical properties

2,4-Pentanedione is a colourless to slightly yellowish liquid (melting point –23°C). It is readily soluble in water (166 g/l at 20°C) and has a vapour pressure of 9.2 hPa (at 20°C) and a density of 0.972 g/cm^3 (at 20°C). The experimental results on water solubility could not be fully validated due to missing information about the test conditions. Based on the structure of the substance, these results are plausible though and can be used in the assessment. The measured low log Kow values of 0.34 and 0.40 indicate no affinity for lipophilic matrices. The two measured Kow results could not be fully validated due to missing information about the test conditions. The KOWWIN, v1.66 software predicts a log Kow of 0.05, which supports the aforementioned measured values.

2 GENERAL INFORMATION ON EXPOSURE

In the EU WACKER CHEMIE GmbH is the only producer of 2,4-pentanedione with an annual production volume of the substance of about 2,900 tons. In the U.S. production figures for the substance have been reported to be in the range of 3,000 – 7,500 tons/a by one company. No further production sites are known. The worldwide production volume is therefore estimated to be about 10,000 t/a.

2,4-Pentanedione is used as a chemical intermediate in the production of pharmaceuticals, dyes and plant protection products. It is also applied in catalyst systems for the polymerisation of olefins and for the control of curing rates in polyurethane coatings. Other uses are found as gasoline and lubricant additives, driers for varnishes and printer inks and colours. The parent compound is also converted to metal-acetoacetonates, which in turn are used as stabilizers in PVC for instance.

2,4-Pentanedione is produced in closed systems. Its synthesis involves thermal rearrangement of isopropenylacetate and distillation of the crude material. The resulting pure substance is transferred and filled into tanks and barrels via pipelines.

Releases into the environment may occur during production and processing of the substance as well as from its direct use.

In the EU, only a minor portion (about 10 %) of the 2,4-pentanedione produced is processed onsite under closed system conditions while the far majority of the material is sold for further processing where it is mainly used for the synthesis of pharmaceuticals, dyes and plant protection products as well as for the production of metal-acetoacetonates. No information is known regarding procedures applied by industrial customers. Production and processing of 2,4-pentanedione at Wacker Chemie GmbH is a waste water free process as stated by the company. Emissions into the atmosphere are also regarded as negligible as the exhaust air is incinerated.

Workplace exposure measurements performed by WACKER Chemie GmbH after analysis of the atmosphere within the production facility itself and during sampling at analytical tanks for quality control purposes 2,4-pentanedione concentrations of less than 7 mg/m^3 were measured in both cases. During filling processes in tanks and barrels no worker exposure does result since all steps are conducted via pipelines.

The Swiss product register gives the information that there is a total amount of 84 products that contain the substance. The products are e.g. paints and lacquers, cleaning agents, hardeners and solvents. 8 products contain the substance in an amount between 1 and 10 %, 10 between 10 and 50 % and 7 between 50 and 100 %. The Danish product register (August 2001) gives the information that there are 53 products that contain the substance in amounts up to 100 %. The product types are solvents, intermediates and process regulators. Among the products there are 2 products for private use. In the Swedish product register (September 2001) there are 20 products, among them 1 product for consumer use, that contain the substance. Main uses are solvents, diluents and paints. Also in the Finnish product register there are 14 products that contain 2,4-pentanedione. The uses are mostly as a paint component (hardener or thinner). The content in paints varies from 5 to 25 %.

No information is available as to residual contents of 2,4-pentanedione in products resulting from downstream uses of the neat substance, e.g. impurities in plant protection or pharmaceutical products and dyes. Therefore, releases into the soil through residual contents in plant protection agents cannot be excluded.

2.1 Environmental Exposure and Fate

According to a Mackay level I model calculation (V 2.11, input parameter: log Kow: 0.34, water solubility: 166 g/l, vapour pressure: 920 Pa) 2,4-pentanedione is mainly distributed to water (ca. 89.8 %) and to a lesser extent into air (ca. 10.1 %).

The relative high degree of distribution into water is based on both the ready water-solubility and the moderate vapour pressure of the substance. According to the criteria of Thomas (1982) the (calculated) Henry's Law constant of 0.555 Pa•m^3/mol indicates a moderate volatility from water (Mackay 1999).

In a MITI I test which corresponds to an OECD 301 C study it could be shown that 2,4-pentanedione is readily biodegradable (79 – 88 % within 28 days) (IUCLID – Existing Chemicals 1999). Due to its chemical structure the substance will not undergo both hydrolysis in water and photodegradation by direct sun-light. At an atmospheric concentration of $1.5x10^6$ hydroxyl radicals/cm^3 and a rate constant of $0.7294x10^{-12}$ cm^3/moleculexsec the half-life of 2,4-pentanedione can be estimated to be about 14 days assuming a 12 h light-cycle. The same result is obtained by assuming an atmospheric concentration of $5x10^5$ hydroxyl radicals/cm^3, a rate constant of $1.15x10^{-12}$ cm^3/moleculexsec and a 24 h reaction time (EPIWIN 2000).

Taking into consideration the measured octanol/water partition coefficients of 0.34 and 0.40 no potential for bioaccumulation/bioconcentration and geoaccumulation can be identified. Assuming a log K_{ow} of 0.40 a calculated bioconcentration factor of 3.162 (log BCF = 0.5) results there from (EPIWIN 2000).

2.2 Human Exposure

2.2.1 Occupational Exposure

Since the material is produced in closed systems, stored and filled in tanks or barrels via pipeline no direct worker exposure does result. In occupational settings, however, exposure towards 2,4-pentanedione might occur during sampling processes for analytical purposes (i.e. quality control) and through the atmosphere within the production facility. Exposure measurements performed in the course of working place surveillance yielded 2,4-pentanedione concentrations of less than the detection limit of 7 mg/m^3 (~1.70 ppm).

One investigator analysed the composition, i.e. the organic solvent content, of 29 printer inks for serigraphy. In only one of 29 inks 2,4-pentanedione was detectable by gas chromatography and the content determined to be 6 % (w/w). However, no data regarding worker exposure to this specific ink component were included in the reference (Rastogi 1991).

For 2,4-pentanedione no working place limit values such as MAK or TLV have been established. It should be mentioned in this context that a co-producer in the US derived a TWA-value (8h) of ~83 mg/m^3 (20 ppm) for the material.

2.2.2 Consumer Exposure

The Swiss product register gives the information that there is a total amount of 84 products that contain the substance. The products are e.g. paints and lacquers, cleaning agents, hardeners and solvents. 8 products contain the substance in an amount between 1 and 10 %, 10 between 10 and 50 % and 7 between 50 and 100 %. The Danish product register (August 2001) gives the information that there are 53 products that contain the substance in amounts up to 100 %. The product types are solvents, intermediates and process regulators. Among the products there are 2 products for private use. Also in the Finnish product register there are 14 products that contain 2,4-pentanedione. The

uses are mostly as a paint component (hardener or thinner). The content in paints varies from 5 to 25 %.

2.2.3 Indirect Exposure via the Environment

No information regarding release to the environment during manufacture and no other environmental background data are available for 2,4-pentanedione. Since the material is produced in closed systems, no or only minimal release to the atmosphere is being implicated. Also, in the absence of monitoring data no information is available concerning indirect human exposure via water, air or foodstuff, respectively.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

No studies are available concerning the mode of action of the substance. It is known, however, that 1,3-diketones unfold metal chelating properties in vivo which may lead to inhibition of enzymatic activity of metal containing enzymes such as peroxidases or cytochrome P450 without concomitantly lowering protein contents.

In an inhalation study conducted in male Fischer 344 rats it could be shown that ^{14}C-labeled-2,4-pentanedione was readily absorbed by the inhalation route. Nose-only exposure to 400 ppm ^{14}C-labeled-2,4-pentanedione resulted in a rapid increase in plasma radioactivity during the first 3 hours of exposure, with a tendency to plateau toward the end of the 6 hour exposure period. Plasma unmetabolized ^{14}C-labeled-2,4-pentanedione was present throughout the whole of the exposure phase, but was significantly less than total ^{14}C. Immediately postexposure, radioacivity was present in all tissues examined, but on a concentration basis (µg equivalents/g) there was no preferential accumulation of ^{14}C in any tissue or organ. On a total organ basis, highest contents were in liver and kidneys. Postexposure, plasma unmetabolized ^{14}C-labeled-2,4-pentanedione declined rapidly to undetectable concentrations by 12 hours. Elimination of ^{14}C from plasma followed a biphasic pattern with a terminal half-life (beta $t_{½}$) of 30.72 hours. Excretion over 48 hours of ^{14}C was approximately equivalent between urine (37.6 %, mainly not identified metabolites) and expired $^{14}CO_2$ (36.3 %), which the most part of the radioactivity was eliminated in the first 12 hours. Expired volatiles, feces, tissues and carcass accounted for 2.29, 2.78, 1.66 and 17.15 % of the total administered radioactivity dose 48 hours postdosing, respectively (Frantz et al. 1998).

3.1.2 Acute Toxicity

The acute toxicity of 2,4-pentanedione was investigated by the oral, dermal and inhalation route, respectively. By either route of administration the material proved to be moderately toxic to the animals tested.

After oral administration to Wistar rats signs of toxicity were characterised by sluggishness, tremors, kyphosis, lacrimation, unsteady gait, comatose appearance and prostration. On histopathology cervical lymph nodes in most animals were enlarged. The LD50-values determined in females and males in this investigation were 570 and 760 mg/kg bw (Ballantyne et al. 1986, Union Carbide Corp. Bushy Run Research Center 1985a).

After inhalation in Wistar rats (4 hours; 628, 919, 1231 and 1508 ppm, respectively, corresponding to 2,619; 3,832; 5,133 and 6,288 mg/m^3) mortalities were observable in animals of the two highest dose groups. Signs of toxicity included reduced reflexes, respiratory difficulties, tremor as well as periocular, perioral and perinasal wetness and encrustation. The combined LC50-value for males and females, respectively, was determined to be 1224 ppm (5.1 mg/l/4h; Ballantyne et al. 1986, Union Carbide Corp. Bushy Run Research Center 1984).

The LD50 of an acute dermal toxicity study after application of undiluted 2,4-pentanedione to the shaved skin of rabbits was in the range of 790 and 1,370 mg/kg bw for female and male animals, respectively. Signs of systemic toxicity were characterised by salivation, dilated pupils and convulsions. In dead animals red mottled lungs and congestion of the tracheal mucosa were observable. Local effects comprised erythema, edema, scab formation and necrosis (Ballantyne et al. 1986, Union Carbide Corp. Bushy Run Research Center 1985a).

Conclusion

All the investigation performed on the acute toxicity of the substance after administration by the oral, dermal and inhalation route show that 2,4-pentanedione has to be regarded as harmful by inhalation, in contact with skin and if swallowed.

3.1.3 Irritation

Skin Irritation

A skin irritation study was conducted in New Zealand White rabbits. A volume of 0.5 ml of undiluted test substance was applied on the dorsal skin of six rabbits (three males and three females, respectively) for 4 hours with occlusive dressing. Treated skin areas were inspected 1 hour and 1, 2, 3, 7 and 14 days after removal of the dressing. The scores were calculated according to Draize.

One hour after removal of the occlusive dressing slight erythema were detectable in 5/6 animals (three males and two females) with an average score of 0.8; after 24 hours erythema were detectable in 6/6 animals (average score 1.0); one hour after removal of the occlusive dressing slight and moderate edema formation was observable in 5/6 and 1/6 rabbits (average score 1.2), respectively; after 24 hours slight edema were still present in 5/6 rabbits (average score 0.8). After 48 and 72 hours five and three animals revealed just detectable erythema (average scores 0.8 and 0.5). Mild edema were observable at 48 and 72 hours in two and one animals, respectively (average scores 0.3 and 0.2). With the exception of mild desquamation detectable in 5/6 animals no skin irritations or other effects were present on day 7 (Ballantyne et al. 1986, Union Carbide Corp. Bushy Run Research Center 1985a). According to the readings made the substance was overall evaluated as not irritating to the skin of rabbits.

However, after repeated dermal application to rabbits local skin irritating effects have been observed (see chapter 3.1.5). Also human data give a hint to a local irritating effects (see chapter 3.1.10).

Eye Irritation

The eye irritation potential of 2,4-pentanedione was investigated in rabbits. A volume of 0.1 ml of undiluted test substance was applied to the eyes of six female New Zealand White rabbits. Eyes were inspected 1, 4, 24, 48 and 72 hours as well as 7 days post-instillation, respectively. The scores were calculated according to Draize. Opacities of the cornea were not detectable at any time. One hour after application of the material, slight redness of the conjunctivae was observable in 5/6 animals (average score 0.8), slight and moderate chemosis in 2/6 and 1/6 animals (average score 0.7), respectively, slight and moderate discharge in 2/6 and 3/6 animals (average score 1.3), respectively, and slight inflammation of the iris in 2/6 animals (average score 0.3). Four hours after application of the material, slight inflammation of the iris was evident in 1/6 animals (score 0.2), slight redness of the conjunctivae in 4/6 animals (average score 0.7), slight and moderate chemosis in 2/6 and 1/6 animals (average score 0.7), respectively, slight and moderate conjunctival discharge was observable in 3/6 and 2/6 animals (average score 1.2), respectively. Twenty-four hours post-instillation all effects seen were completely reversible (Ballantyne et al. 1986, Union Carbide Corp. Bushy Run Research Center 1985a). On the basis of the readings made throughout the study the material resulted in minor transient irritation with no corneal involvement. According to the grading system available the material has not to be evaluated as an eye irritating substance. However, there are some human data on eye irritating from large application (see chapter 3.1.9).

3.1.4 Sensitisation

Skin

The skin sensitising properties of 2,4-pentanedione were examined in five guinea pigs and in a human patch test consisting of 12 volunteers.

No detailed description of the methods applied was available for both the animal and human patch test study. It was reported that five guinea pigs were treated on the basis of a standardised skin sensitisation test and 1/5 guinea pigs revealed a weak response while the remaining 4/5 animals remained normal. The overall result of the study was evaluated as ambiguous by the study authors (Eastman Kodak 1979). In the patch test study with human volunteers no information was available concerning gender and health status as well as a possible allergic predisposition of the test persons. Of the 12 persons tested three of them showed no, seven doubtful and two a positive reaction after an exposure period of 24 hours. No skin reactions were evident after 48 and 72 hours, respectively. The results observed in the human patch test were interpreted as an irritating rather than a sensitising effect and it was concluded by the authors that sensitisation might occur more frequently due to prolonged and close skin contact of pads containing the substance (Sterry and Schmoll 1985). However, due to both the poor description of the study and the very weak irritating potential of the compound a verification of the results described is lacking.

Overall, a sensitising potential of the substance can neither be excluded nor assumed on the basis of this data.

3.1.5 Repeated Dose Toxicity

The toxicity of 2,4-pentanedione was investigated by the oral, dermal and inhalation route of administration, respectively.

Oral administration (Eastman Kodak 1979)

In the oral study, doses given by gavage to rats (5 animals per group, strain and sex not specified) were 0, 100, 500 and 1,000 mg/kg bw, respectively. Test substance was administered for 1-15 days in 1-11 applications. In the highest dose group all animals died within 1 hour after dosing. In the 500 mg/kg bw group 3/5 animals died and 2/5 were sacrificed due to poor condition after four applications. Various substance related systemic effects were observable in this dose group such as distended bladder, congested lungs, clouding of cornea, thymic necrosis, hepatocyte swelling and congestion, nephrosis, lymphadenitis of mesenteric lymph nodes and inflammation of the heart. In the lowest dose group (100 mg/kg bw) no histopathological or gross pathological changes and no differences in weight gain, organ weights, hematology, clinical chemistry or clinical signs were evident. The lowest dose of 100 mg/kg bw was applied 10 times over a 14 days period. According to the results of this study a NOAEL of 100 mg/kg bw could be derived.

Dermal administration (Ballantyne 2001, Union Carbide Corp. Bushy Run Research Center 1995)

Male and female New Zealand White rabbits were treated dermally under occluded conditions with doses of 244, 975 and 1,463 mg/kg bw, respectively, for 9 days (5 days first week and 4 days second week). Six animals/sex/group were used in the low and mid dose group, 12 animals/sex/group in the control and high dose group. Application of 1,463 mg/kg bw resulted in death of approx. 50 % of animals of either sex while in the mid dose group 1/6 males and 3/6 females died. Beside local skin irritating effects evident in all dose groups such as acanthosis, subcutaneous edema, dermatitis, hemorrhage, congestion and/or necrosis, only in the mid and high dose group systemic toxicity was observable and characterised by hypoactivity, prostration, salivation, tremors, gasping, convulsions and cyanosis as derived from blue cutis of the nasal area. Pathological examination of the mid and high dose animals identified the brain as a target with

hemorrhage and neuronal degeneration in several sections of this organ. On both day 4 and 12, the thymus or thymic region, spleen and/or lymph nodes of several animals of both sexes from the mid and high dose groups were congested and/or hemorrhaged; some animals also had lymphoid depletion/necrosis. In the opinion of the authors, this observation, combined with decreased lymphocyte and eosinophil counts in the high dose group at day 4, suggested possible effects on the immune system. Since the animals from the mid and high dose group had severe skin irritation and many signs of systemic effects a definitive conclusion regarding a treatment related response to the immune system is not possible. In contrast, no substance related differences from controls were reported in the low dose group. According to the systemic effects observed 244 mg/kg bw and 975 mg/kg bw correspond to the NOAEL and LOAEL of this dermal study, respectively.

Administration by Inhalation (Dodd et al. 1986, Union Carbide Corp. Bushy Run Research Center 1984, 1985b)

In a 14 weeks inhalation study 20 male and 20 female F344 rats per dose were exposed to 0, 100, 300 and 650 ppm (nominal concentrations, corresponding to 0; 417; 1,217 and 2,711 mg/m^3) of 2,4-pentanedione vapour for 6h/d, 5d/w. 10 animals per sex and dose group were included for a four weeks recovery period and additional 10 animals were added to the control and high dose group for glutaraldehyde perfusion and subsequent examination of sciatic nerves. Test substance concentrations were monitored every 33 minutes during the daily 6 h exposure.

In the 650 ppm group all females and one third of the males died during the 2nd and 6th week. In this dose group several clinical abnormalities such as lacrimation, ataxia, hypoactivity and hypothermia were observable. Surviving animals of the 650 ppm group showed decreased body weight gains, decreased absolute organ weights (brain, liver, kidney, heart, lungs), but increased relative organ weights, and minor alterations in hematology (i.e. reduced hematocrit and red blood cell counts, increased mean corpuscular hemoglobin and volume and increased lymphocytes), serum chemistry and urinary chemistry. On (histo)-pathological examination acute degeneration in the deep cerebellar and vestibular nuclei, in the corpora striata and acute lymphoid degenerations in the thymus were noteworthy lesions in dead animals of the 650 ppm exposure group. Survivors of this exposure group had gliosis and malacia in the same brain regions but no peripheral neuropathy, minimal squamous metaplasia in the nasal mucosa, and lymphocytosis. Most of the observable substance related effects in the 650 ppm group decreased in frequency and severity during the four weeks recovery period in surviving animals.

In the 100 ppm group there were no substance related mortalities in either sex and on comparison with untreated controls no differences in clinical and urinary chemistry, hematology or after histopathological examination were detectable. In the 300 ppm group minor alterations in haematology, serum (serum calcium) and urine chemistry were observable in rats of both sexes while slight decreases in body weight gains (final body weight 5 % decreased) were found in females of this dose group only. All effects in this dose group were completely reversible during the four weeks recovery period and no statistically significant differences between absolute body weight means for controls and the 300 ppm group were observable. Consequently, based on the reversibility of effects in the 300 ppm group the NOAEL, LOEL and LOAEL of this study is defined to be 100 ppm (417 mg/m^3), 300 ppm (1,217 mg/m^3) and 650 ppm (2,711 mg/m^3), respectively. These doses can be converted to a NOAEL of 144.1 mg/kg bw/d, a LOEL of 432.3 mg/kg bw/d and a LOAEL of 936.7 mg/kg bw/d assuming a respiratory minute volume of 0.24 l/min (14.4 l/h) and an average weight of 250 g/rat.

An inhalation study in male and female F344 rats applied a two weeks exposure regimen with inclusion of a two days non-exposure period, i.e. a total of 9 exposures (5 days and 4 days). Nominal concentrations were 0, 200, 400 and 800 ppm (corresponding to 0; 834; 1,668 and 3,336 mg/m^3) of 2,4-pentanedione vapour, respectively, and test substance concentrations were metered every 33 minutes throughout the exposure period. No substance related mortalities were

found in any of the exposure groups. Body weight gains were reduced in either sex of the 800 ppm group and in males only of the 400 ppm group (2 – 4 %) while in the 200 ppm group no differences from control body weight gains were detectable. Absolute organ weights were reduced in the 800 ppm group for brain, liver, kidneys, lungs/bronchi and thymus. Relative thymus weights were decreased in the 800 ppm males and females. In the 400 ppm group thymus weights in male animals only were lowered (15 % absolute, 11 % relative) and no differences from controls were found in the lowest exposure group of 200 ppm. At 800 ppm leucocytosis in both sexes and a statistically significant increase in lymphocyte count, increased mean corpuscular hemoglobin concentration and mean corpuscular hemoglobin in male rats were detected. Hemoglobin alterations were considered not to be toxicologically significant. No differences from control animals were found for hematological parameters in the 200 and 400 ppm exposure group, respectively. On histopathological examination no gross lesions were observable in any of the exposure groups. A dosage related irritation, manifested as inflammation, congestion and superficial necrosis of the upper respiratory tract, was observed in all 2,4-pentanedione treated groups. Necrosis of the nasal mucosa was frequently observed in the 800 ppm group, occasionally in the 400 ppm group and absent in the 200 ppm group. The degree of mucosal epithelial vacuolisation and lymphocytic infiltration in the submucosa appeared exposure-related. No lesions were found in the lower respiratory tract. Based on the reduction of thymus weights in males of the 400 ppm exposure group the NOAEL and LOAEL of the study is defined to be 200 and 400 ppm, respectively, corresponding to 288.2 mg/kg bw/d and 576.4 mg/kg bw/d assuming a respiratory minute volume of 0.24 l/min (14.4 l/h) and an average weight of 250 g/rat.

In conclusion after administration by the oral route substance related systemic effects were evident in thymus, liver, lungs, kidneys, bladder and lymph nodes.

Beside unspecific central nervous symptoms and irritation in the nasal mucosa and both irritation and inflammation of the respiratory tract substance related systemic effects after inhalation were characterized by changes in hematology, clinical and urinary chemistry as well as organ changes in the region of the brain and thymus. On repeated dosing via the dermal route beside local skin irritating effects signs of toxicity were evident as hemorrhage and neuronal degeneration in the region of the brains as well organ changes or hemorrhage in spleen, thymus and lymph nodes. In a 14-week inhalation study the NOAEL was 417 mg/m^3 and the LOAEL 2711 mg/m^3.

3.1.6 Mutagenicity

In vitro Studies

Bacterial test in vitro

The mutagenicity of 2,4-pentanedione was investigated in a standard AMES test using *S. typhimurium* strains TA98, 100, 1535, 1537 and 1538 both in the presence and absence of a metabolic activation system (liver S9 mix produced from rats pretreated with Aroclor 1254). The test was conducted according to currently valid guidelines. The test material did not produce a statistically significant increase in the revertants / plate (less than doubling) thereby demonstrating no potential of 2,4-pentanedione to induce gene mutations (Union Carbide Corp. Bushy Run Research Center 1985c).

Another AMES test was conducted in *S. typhimurium* strains TA92, 98, 100 and 104 in the absence of a metabolic activation system. Water or DMSO served as solvent (negative) controls, potassium dichromate (10 µg/plate), methylmethansulfonate (2 µg/plate) and hycantone (20 µg/plate) served as positive controls. No information was given as to the concentration ranges of 2,4-pentanedione used in strains TA92, 98 and 100 where no mutagenic effects were reported. Test concentrations in the strain TA104 were 1.9 – 48 µmol/plate, substance was added in water or DMSO (not specified in the reference available) in a volume of 0.1 ml. According to the results observed and considering

the rates of spontaneous revertants for this particular strain (400 – 700 revertants), 2,4-pentanedione has to be considered only slightly mutagenic in TA104 at concentrations ranging from 1.9 – 10 µmol/plate, were the number of revertants/plate increased to its maximum of 1500, which is in contrast to the evaluation of the authors classifying the substance as "strongly mutagenic". At concentrations > 10 µmol/plate, no significant increase in the number of revertants compared to control values could be observed. Thus the increase of revertants/plate was not in a dose-response relationship (Gava et al. 1989).

Non-bacterial test(s) in vitro

The genotoxicity of 2,4-pentanedione was studied in a series of in vitro assays using mammalian cells (CHO cells) and investigating different endpoints such as sister chromatid exchanges (SCE), chromosomal aberrations (CA) and gene mutations (HGPRT-test). All tests performed correspond to current valid methodologies assessing the genotoxic potential of substances.

In the SCE-assay 2,4-pentanedione produced a statistically significant increase in the number of SCE/cell at concentrations not causing overt cytotoxicity both in the presence and absence of a metabolic activation system (liver S9 mix produced from rats pretreated with Aroclor 1254). Highest test substance concentrations employed in this test were 0.1 and 0.3 mg/ml and exposure times were 5 h and 2 h in the absence and presence of a metabolic activation system, respectively. Additionally, it was found that 2,4-pentanedione was considered genotoxic particularly in the absence of metabolic activation since the magnitude of SCE induction was lower when activation by S9 mix was included (Union Carbide Corp. Bushy Run Research Center 1986c).

In a forward-gene-mutation assay (HGPRT-test) 2,4-pentanedione did not cause any statistically significant increases in the incidence of mutations in CHO-cells at the HGPRT-locus both in the presence and absence of a metabolic activation system (liver S9 mix produced from rats pretreated with Aroclor 1254). The highest substance concentrations in this test were 1.5 and 1.0 mg/ml in the absence and presence of metabolic activation, respectively. The exposure time was 5 h with and without activation followed by a 9 – 12 days subculturing period to allow expression of the mutant phenotype. In addition, it was demonstrated that random cultures with increased mutant values were within the typical range of variability (Union Carbide Corp. Bushy Run Research Center 1986d).

The ability of 2,4-pentanedione to induce chromosomal aberrations was investigated in cytogenetic tests using CHO-cells both in the presence and absence of a metabolic activation system (liver S9 mix produced from rats pretreated with Aroclor 1254). In the first study maximum substance concentrations employed were 0.03 mg/ml and 0.1 mg/ml with and without activation and did not cause excessive cytotoxicity or inhibition of mitotic cells. Cells were exposed to the test substance for 2 h with and 6 or 10 h without activation. Results obtained in this study were inconsistent and characterised by small increases in chromosomal aberrations (simple chromatid breakage) with and without activation by liver S9 mix (Union Carbide Corp. Bushy Run Research Center 1986e). Since the test substance could not definitively be classified as a clastogen a second study (repeat study) was performed for clarification. The highest test substance concentrations in the second investigation were 0.12 mg/ml and 0.14 mg/ml in the absence and presence of metabolic activation and did not produce excessive cytotoxicity. Exposure times of cells towards test substance were 2 h and 6 h with and without metabolic activation, respectively. In the absence of S9 activation a test substance related increase in the number of chromosomal aberration was observable as indicated by chromosome breakage while in the presence of activation thereby mimicking more physiological and realistic conditions no clastogenicity was found under the conditions of the experimental procedure (Union Carbide Corp. Bushy Run Research Center 1986f).

Conclusion:

2,4-pentanedione was not mutagenic in bacterial test systems (except slightly mutagenic effect in Salmonella typhimurium TA104) and in mammalian test systems in vitro. It showed a weak

clastogenic activity in mammalian cells in vitro in the absence of metabolic activation, but not in the presence of metabolic activation.

In vivo Studies

2,4-pentanedione was studied for its potential to produce chromosomal aberrations and micronuclei in male and female ND4 Swiss Webster mice as well as male and female Sprague-Dawley rats after inhalation.

Male and female Swiss Webster mice were exposed to 0 (10 animals per sex), 100 (10 animals per sex), 400 (10 animals per sex) and 600 ppm (14 animals per sex) of 2,4-pentanedione vapour for five consecutive days, 6 h/day by whole body exposure. These concentrations correspond to 0; 417; 1,668 and 2,502 mg/m^3. The highest dose of 600 ppm corresponded to about 50 % of the LC_{50}-value determined in acute inhalation toxicity studies in rats (Union Carbide Corp. Bushy Run Research Center 1984). Air-only controls (10 animals per sex) and a well established positive control (i.p. administration of cyclophosphamide monohydrate, five animals per sex) was included in this assay. Bone marrow from 2,4-pentanedione and air-control treated animals was collected 6 h and 24 h after the end of the exposure period while bone marrow from positive controls was collected after 24 h only. Colchicine was dosed by intraperitoneal injection (4 mg/kg) two to three hours prior to sacrifice. In the 600 ppm exposure groups only two females assigned to the bone marrow collection times of 6 h and 24 h survived until the scheduled sacrifice. Signs of toxicity in female animals of the 600 ppm exposure group were characterised by prostration. In all other doses groups no treatment related adverse effects were found. It could be demonstrated that 2,4-pentanedione did not increase the number of chromosomal aberrations in a statistically significant manner. Therefore, the material is not considered to be clastogenic under the conditions of the inhalative in vivo assay (Union Carbide Corp. Bushy Run Research Center 1994a).

Ten animals (Sprague-Dawley rats) per sex and dose group were exposed to 0, 100, 400 ppm (corresponding to 0; 417 and 1,668 mg/m^3) of 2,4-pentanedione vapour for five consecutive days, 6 h/day. Fourteen animals per sex (7 per harvest time) were exposed to 800 ppm (corresponding to 3,336 mg/m^3). The doses were chosen based on the results of previous acute and repeated exposure studies. For positive control Cyclophosphamide was administered as a single injection to 5 male and 5 female rats. Due to unexpected mortalities among male and female rats exposed to the 800 ppm target concentration, that target concentration was lowered after the second exposure day to 650 ppm (2,711 mg/m^3) for the surviving male rats. Eleven out of the fourteen female rats exposed to 2,4-pentanedione at 800 ppm died after the second exposure and the three remaining moribund female rats were euthanized. An additional target concentration of 600 ppm (2,502 mg/m^3) was added to the study and was administered to both male and female rats by whole body exposure to vapour 6 hours per day for 5 consecutive days. Ten animals per sex (5 at each harvest time) were sacrificed 6 or 24 hours after the fifth exposure, the cyclophosphamide treated animals were sacrificed at the same time as the 24 h post-2,4-PD treatment group. Bone marrow cells were harvested and evaluated for chromosomal damage. 2,4-Pentanedione produced one statistically significant increase in the incidence of chromosomal aberrations in male rats exposed at a target concentration of 100 ppm as compared to air-exposed (negative control). There were no statistically significant increases in the incidence of chromosomal aberrations among male rats exposed at target concentrations of 400, 600 or 800 ppm. No statistically significant or concentration-related increases in the incidence of chromosomal aberrations were observed among 2,4-PD-exposed female rats. Because the statistically significant observation among male rats exposed at 100 ppm was small in magnitude (5,2 %) and did not persist at the 24 h sacrifice, 2,4-PD was not considered to have biologically significant clastogenic activity in rats under the conditions of this test by the authors of the report (Union Carbide Corp. Bushy Run Research Center 1990).

When male and female Swiss Webster mice as well as male and female Sprague-Dawley rats (5/sex at the groups for air-only control, positive control, 100 ppm, 400 ppm, 600 ppm) were exposed to

2,4-pentanedione vapour under identical conditions (exposure concentrations 0, 100, 400 and 600 ppm; corresponding to 0; 417; 1,668 and 2,502 mg/m³, respectively; exposure period 5 days, 6 h/d) and bone marrow was collected 24 h after final exposure and examined for the formation of micronucleated polychromatic erythrocytes (PCEs) no statistically significant increases in the incidence of micronucleated PCEs could be found in any of the dose groups administered. In the highest exposure concentration of 600 ppm 3/5 female mice and 3/5 female rats died and substance related effects in this dose group were evident as hypoactivity, prostration, urogenital wetness, gasping, slow respiration and blepharospasm (Union Carbide Corp. Bushy Run Research Center 1993).

The potential of 2,4-pentanedione to induce micronuclei was investigated in male and female Swiss Webster mice after i.p. administration. Five mice per sex and dose group were used, doses administered were 0, 200, 400 and 650 mg/kg bw corresponding to 25, 50, and 80 % of the i.p. LD_{50}, respectively. A negative (water) and a positive control (triethylenemelamine) was included in this assay. Blood samples were taken 30, 48 and 72 h after treatment with 2,4-pentanedione for the evaluation of micronucleated PCEs while blood samples from positive controls animals were subjected to PCE analysis after 30 h only.

At 30 and 48 h, respectively, a statistically significant increase in the number of micronucleated PCEs was detectable in a dose dependent manner while the number of PCEs with micronuclei was not different from controls in the 72 h blood samples. Regardless of dose and time of blood collection no influence on the PCE/NCE ratio was observable while a significant decrease of the PCE/NCE ratio was found in the positive controls.

In conclusion 2,4-pentanedione induces micronuclei in mice of both sexes after administration by the i.p. route (Union Carbide Corp. Bushy Run Research Center 1986g).

The capability of 2,4-pentanedione to induce micronuclei was investigated in male and female Sprague-Dawley rats after i.p. administration, too. On the basis of the description available, the study was conducted according to current guidelines. Five animals per sex and dose were used in this study and a total of five dose groups (50, 100, 200, 400 and 650 mg/kg bw, corresponding to 6.5, 13, 26, 52, and 86 % of the oral LD_{50}, respectively) was administered to the animals as a single i.p. injection. The two lowest dose groups of 50 and 100 mg/kg were included because of mortalities in the 400 and 650 mg/kg dose groups. Substance related signs of toxicity in the 400 and 650 mg/kg groups included hypoactivity, incoordination, prostration, whole body tremor, tonic convulsions, excessive vocalization, urogenital area wetness, labored respiration, gasping, perinasal and perioral wetness, nasal discharge, periocular encrustation and lacrimation. In the other dose groups no (50 and 100 mg/kg bw) or less pronounced (200 mg/kg bw) signs of toxicity were reported. Following a single administration by i.p. injection 2,4-pentanedione did not produce statistically significant, treatment related increases in the incidence of micronucleated polychromatic erythrocytes in male and female Sprague-Dawley rats as assessed at 6, 24 and 48 hours (Union Carbide Corp. Bushy Run Research Center 1994b).

The capability of 2,4-pentanedione to induce germ cell mutations was studied in a dominant lethal assay in male F344 rats by the inhalation route of exposure. Dose ranges included 0, 100, 400 and 700 ppm (corresponding to 0; 417; 1,668 and 2,919 mg/m^3), respectively, and 20 animals per dose group were exposed to test substance vapour for 5 consecutive days, 6 h/d. After the last exposure treated males were paired with naive females (two females with one male) of the same strain for eight consecutive weeks and observed for evidence of copulation. Females without evidence of breeding (copulation plug or vaginal smear) were removed and replaced weekly. After eight weeks brains, testes as well as thymus of males were removed for histopathological examination.

Males exposed to 400 and 700 ppm test substance showed reduced body weights at week 1 and only males of the highest exposure group still showed reduced body weights one week after

termination of exposure. Due to stress by inhalation exposure weight loss was evident in animals of all dose groups. No treatment related clinical signs of toxicity and no microscopic lesions were found on histological examination of brain, testes and thymus in any of the exposure groups. Signs of toxicity were restricted to males of the 700 ppm only and included aggression, red ocular discharge and red perioral encrustation. Reproductive parameters for males and females were affected only on week 3 where the number of pregnant females was slightly reduced at 400 and 700 ppm resulting in a lowering of the female fertility index. Gestational parameters were affected on weeks 2 and 4 of mating and characterised by a reduction of the corpora lutea per dam in week 2 and a reduction in the number of total and viable implants per dam both in week 2 and 4 at 700 ppm. In week 2 postimplantation loss was slightly but not statistically significantly increased at 400 and 700 ppm and preimplantation loss was significantly increased in week 4. Although there was weak statistical significance of the 700 ppm value, the very high s.d. in both cases indicates high variability of the data from individual animals. A clear evaluation of substance related dominant lethal effects is not possible on the basis of the results of the study (Tyl et al. 1989, Union Carbide Corp. Bushy Run Research Center 1986h).

In a mouse spermatogonial assay 2,4-pentanedione was administered in deionised water to 6 male NMRI mice at a dose of 800 mg/kg bw and spermatogonial cells of 5 animals/dose prepared 24 and 48 hours after administration. The dose selected was close to the MTD as shown in a preceding range-finding test and caused signs of toxicity such as reduction of spontaneous activity, eyelid closure, apathy and tremor. The bioavailability of the material was ensured in a preceding study as well. The vehicle (deionised water) and adriblastin served as negative and positive controls, respectively.

100 cells per animal (i.e. 500 cells per time point) were examined for chromosomal aberrations. Neither a reduction in mitotic indices nor an increase in the number of numerical or structural chromosomal aberrations were detectable in the substance treated group when compared with vehicle treated controls while pronounced effects were caused by adriblastin. 2,4-pentanedione is considered non-clastogenic to germ cells under the conditions of the assay (RCC-CCR 2000).

Conclusion

If given by the inhalation route no genotoxic effects were observed in a consistent fashion. In contrast, after i.p. administration no consistent genotoxic responses were observable with the rat showing no genotoxicity while the results with mice were positive.

3.1.7 Carcinogenicity

To date, no studies concerning the long-term toxicity and/or carcinogenic potential of 2,4-pentanedione have been conducted.

3.1.8 Toxicity for Reproduction

Reproductive Toxicity

No animal studies were conducted with 2,4-pentanedione to investigate possible substance-related effects on the reproductive performance. In a subchronic inhalation study conducted in male and female F344 rats after exposure towards 0, 100, 300 and 650 ppm (nominal concentrations, corresponding to 0; 417; 1,217 and 2,711 mg/m^3) no findings of pathological significance were noted in testes and epididymis of males as well as in uterus, cervix and ovaries of females on comparison with untreated control animals both immediately after study termination and after a four week recovery period, respectively, thereby revealing no adverse effects on male and female reproductive organs (Dodd et al. 1986, Union Carbide Corp. Bushy Run Research Center 1985b). In males one/10 control animals of the recovery group was diagnosed with epididymitis while in

females of the recovery group ovarial cysts ("cystic ovarian bursa") were found in 2/10 animals of the control group but none in the treated groups. One/10 animals each of the control and intermediate dose group (300 ppm) had changes in uterus size ("luminal ectasia") while 1/10 animals of the intermediate dose group (300 ppm) had size changes in the cervix ("luminal ectasia"). Based on the overall findings made in this inhalation study the NOAEL and LOAEL were 100 and 650 ppm, respectively. The NOAEL for effects on gonadal tissues was 650 ppm (see chapter 3.1.6). In addition, a most recent study conducted to test the genotoxicity of the material on germ cells in a mouse spermatogonia drinking water assay clearly demonstrated the absence of substance associated adverse effects on murine germ cells at a dose close to the MTD supporting observations made on the non-adverse effects of the material to rat testes in repeated dose inhalation studies (RCC-CCR 2000).

Developmental Toxicity

(Union Carbide Corp. Bushy Run Research Center 1986b)

25 timed-pregnant F344 rats per dose group were exposed to nominal concentrations of 0, 50, 200 and 400 ppm (corresponding to 0; 209; 834 and 1,668 mg/m^3) of 2,4-pentanedione vapour, respectively, through organogenesis (gestation days 6-15) to evaluate the embryotoxic, fetotoxic and teratogenic potential of the test material. Chamber concentrations of test substance were metered on a regular basis throughout the study. To produce a sufficient number of gravid females untreated male and female rats were mated in a 1:1 fashion. Dams were examined for body weight, liver and thymus weights, gravid uterine weight, status of implantation sites (i.e. resorptions, dead and live fetuses) and maternal brains were examined histopathologically. Live fetuses were removed from the uterus, counted, weighed, sexed and evaluated for external abnormalities. Visceral abnormalities, craniofacial malformations and skeletal defects were examined in exposed as well as in control animals.

Apart from a significantly reduced body weight gain in the 400 ppm exposure group (transient reduced body weight on gestation days 9, 12, 15 and 18 but not on gestation day 21, and reduced weight gain for the intervals gestation days 6-9, 6-12, 6-15 (exposure period) and gestation days 6-18, but not for the postexposure period on gestation days 15-21) no treatment related effects on body weights, liver weights, thymus weights and gravid uterine weights were observable in any dose group at the time of sacrifice as was histopathological examination of the brains. No substance related effects on the number of corpora lutea, on total, non-viable and viable implantations per litter, pre- or postimplantation loss or sex ratio was detectable. Also, there were no maternal deaths, early deliveries or abortions.

Fetotoxicity was manifested by reduced fetal weights in both sexes (approximately 10 %) and a consistent pattern of reduced fetal ossification at 400 ppm and by reduced fetal weights in male fetuses at 200 ppm (approximately 3 %), respectively. There was no evidence of embryotoxicity and the incidences of variations by category (external, visceral including craniofacial, and skeletal) or of total variations as well as incidences of external, visceral and skeletal malformations did not differ among groups including those producing maternal toxicity.

Based on a significantly reduced body weight gain in the 400 ppm exposure group the NOAEL/LOAEL derived for maternal toxicity is 200 and 400 ppm (= 834 / 1,668 mg/m^3 = 288.2 / 576.4 mg/kg bw/d assuming a respiratory minute volume of 0.24 l/min and an average weight of 250 g/rat), respectively. The NOAEL for developmental toxicity is 50 ppm (= 209 mg/m^3 = 72.2 mg/kg bw/d), respectively, which is based on reduced fetal weights in male fetuses at 200 and in male and female fetuses at 400 ppm and a consistent pattern of reduced fetal ossification at 400 ppm.

Conclusion

There is no reproductive toxicity study, however the investigations of the reproductive organs of a 14-week inhalation study in rats did not show any effects. Concerning effects on germ cells a dominant lethal assay showed slight but not clear effects on fertility parameters in the (untreated) pregnant females mated with substance treated males being exposed via the inhalation pathway. In an in vivo mouse spermatogonia assay 2,4-pentanedione did not produce chromosomal aberrations after oral administration to male mice at a dose close to the MTD.

2,4-pentanedione showed no teratogenic activity. Fetotoxic effects (reduced fetal weights in male fetuses) were observed at 200 ppm without signs of maternal toxicity. In addition, at 400 ppm (reduced fetal weights in fetuses of both sexes and reduced fetal ossification) reduced maternal weight also occurs.

3.1.9 Human data

Regarding effects on humans only very little information is available. In the public literature it is described that exposure of humans towards 2,4-pentanedione vapour may cause unspecific effects such as dizziness, headache, nausea, vomiting and loss of consciousness. Skin irritation appears less hazardous and effects are mild while eye burns similar to soap may result from a large application (HSDB 2000). It is also reported that the material causes slight local irritant effects which are readily reversible and disappear after the end of exposure. In humans the substance reveals moderate systemic effects after inhalation which do not lead to death or permanent injury due to the low degree of severity (HSDB 2000).

However, since this data are difficult to evaluate due to poor description of the results and the animal experiment show a weak if any local irritation after single application, which is more pronounced only after prolonged exposure (see chapter 3.1.3 and 3.1.5).

In a patch test study with human volunteers no information was available concerning gender and health status as well as a possible allergic predisposition of the test persons. Of the 12 persons tested three of them showed no, seven doubtful and two a positive reaction after an exposure period of 24 hours. No skin reactions were evident after 48 and 72 hours, respectively. The results observed in the human patch test were interpreted as an irritating rather than a sensitising effect and it was concluded that sensitisation might occur more frequently due to prolonged and close skin contact of pads containing the substance (Sterry and Schmoll 1985). However, due to both the poor description of the study and the very weak irritating potential of the compound a verification of the results described is lacking.

3.2 Initial Assessment for Human Health

Production and processing:

2,4-Pentanedione is produced by WACKER Chemie GmbH in closed systems in quantities of about 2,900 tons a year. Figures reported by the American co-producer Union Carbide Corporation are in a range of 3,000 - 7,500 tons a year. No further production sites are known. The worldwide production volume is therefore estimated to about 10,000 t/a.

The material produced in the sponsor country is used as an intermediate in the production of dyes, pharmaceuticals, plant protection products and metallo-acetoacetonates which find use as stabilizers in PVC for instance. Production and processing of 2,4-pentanedione at Wacker Chemie GmbH is a waste water free process as stated by the company. Emissions into the atmoshere are also regarded as negligible as the exhaust air is incinerated. No data are available regarding release to the environment at other production and processing sites.

Product register information indicates that products may contain the substance in considerable amounts. Product types are e.g. paints and lacquers, cleaning agents and solvents. Among the products there are several for private use.

Human Health:

In acute toxicity studies the material proved to be moderately toxic after administration by the oral, dermal and inhalation route, respectively:

LD_{50} (oral, rat) = 570/760 mg/kg bw (f/m)

LC_{50} (inhalation, rat) = 5.1 mg/l/4 h (1244 ppm)

LD_{50} (dermal, rabbit) = 790/1,370 mg/kg bw (f/m)

The values obtained show that 2,4-pentanedione has to be regarded harmful by inhalation, in contact with skin and if swallowed.

Also, animal studies on the primary irritancy of the substance demonstrated a low, if any irritation potential both to the skin and eyes after single exposure not leading to a classification as a skin and/or eye irritant. After repeated dermal application to rabbits local skin effects have been observed. Human data give a hint to a local irritating effect.

Based on the poor data available the sensitising potential of 2,4-pentanedione cannot be evaluated.

In a 14 week repeated dose inhalation toxicity study in rats 2,4-pentanedione exerted substance related effects on haematological parameters, clinical and urinary chemistry at doses of 300 and 650 ppm (1,217 and 2,711 mg/m^3), respectively. On histopathology, no substance related gross lesions were detectable in the organs examined in all dose groups with the exception of different regions in the brain where hemorrhage and neuronal degeneration was observable and lymphoid degeneration in the thymus at a dose of 650 ppm. In this study no pathological findings were made in the reproductive organs of animals of both sexes, especially in the testes of males. Based on the reversibility of haematological, clinical as well as urinary chemical effects in the 300 ppm group and the histopathological findings in the brains and thymus in the 650 ppm group the NOAEL, LOEL and LOAEL of this study is defined to be 100 ppm (417 mg/m^3), 300 ppm (1,217 mg/m^3) and 650 ppm (2,711 mg/m^3), respectively. These doses can be converted to a NOAEL of 144.1 mg/kg bw/d, a LOEL of 432.3 mg/kg bw/d and a LOAEL of 936.7 mg/kg bw/d assuming a respiratory minute volume of 0.24 l/min and an average weight of 250 g/rat. After repeated treatment of rabbits dermally, effects on thymus, spleen and lymph nodes haemorrhage and neuronal degeneration in several sections of the brain were seen. After administration by the oral route substance related systemic effects were evident in thymus, liver, lungs, kidneys, bladder and lymph nodes.

No mutagenic effects were seen in the Ames test (except slightly mutagenic effect in *Salmonella typhimurium* strain TA104) and in the HPRT-assay. A positive clastogenic effect in CHO cells was observed in the absence of metabolic activation, but not in the presence of metabolic activation. All in vivo genotoxicity studies conducted in rats and mice by inhalation did neither increase the number of structural or numerical aberrations nor the number of micronuclei. In contrast 2,4-pentanedione was shown to produce statistically significant increases in the incidence of micronucleated PCEs in mice but not in rats after i.p. administration. Concerning effects on germ cells a dominant lethal assay showed slight but not clear effects on fertility parameters in the (untreated) pregnant females mated with substance treated males being exposed via the inhalation pathway. In an in vivo mouse spermatogonia assay 2,4-pentanedione did not produce chromosomal aberrations after oral administration to male mice at a dose close to the MTD. Overall 2,4-pentanedione shows a direct clastogenic potential in vitro which is not expressed in vivo by the inhalation route.

There is no reproductive toxicity study, however the investigations of the reproductive organs of a 14-week inhalation study in rats did not show any effects. The reported effects in the dominant lethal test in rats were evaluated as not induced by the substance. No chromosomal aberrations were observed in spermatogonia of mice.

In an inhalation teratogenicity study in female F344 rats the material did not produce teratogenic effects. Fetotoxic effects (reduced fetal weights in male fetuses) were observed at 200 ppm (= 834 mg/m^3) without signs of maternal toxicity. In addition, at 400 ppm (1,668 mg/m^3) reduced fetal weights in fetuses of both sexes and a consistent pattern of reduced fetal ossification as well as reduced maternal weight occurs. The NOAEL for maternal toxicity was 200 ppm (= 834 mg/m^3 = 288.2 mg/kg bw/d assuming a respiratory minute volume of 0.24 l/min and an average weight of 250 g/rat) based on total resorption of litters in two dams and significantly reduced body weight gain in the 400 ppm group only. The NOAEL for developmental toxicity was determined to be 50 ppm (= 209 mg/m^3 = 72.2 mg/kg bw/d assuming a respiratory minute volume of 0.24 l/min and an average weight of 250 g/rat), which is based on reduced fetal weights at 200 and 400 ppm and a consistent pattern of reduced fetal ossification at 400 ppm.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

The acute aquatic toxicity of 2,4-pentanedione to fish has been investigated in several species of fresh water fish. In flow-through studies with analytical monitoring the material showed a minimum 96 h LC_{50} of 60.1 mg/l in the bluegill (*Lepomis macrochirus*) (C.I. 50.3 – 71.8 mg/l) and a maximum 96 h LC_{50} of 175 mg/l in the fathead minnow (*Pimephales promelas*) (Thurston et al. 1985, Brooke et al. 1984).

The acute toxicity of 2,4-pentanedione was studied in several static tests with *Daphnia magna*. The 48 h EC_{50}-values obtained from these studies were 34.4 mg/l (nominal), 48 mg/l (measured) and 75 mg/l (nominal) thereby showing good comparability of all tests (Thurston et al. 1985, Mount and Norberg 1984, Bringmann and Kuehn 1982, Elnabarawy et al. 1986).

The acute aquatic toxicity of the substance was investigated in the algal species *Scenedesmus sp*. After an exposure time of 24 hours the EC_{10}- and EC_{50}-values were determined to be 100 mg/l and > 300 mg/l, respectively (Krebs 1985). The EC_{10}-value from this test can be regarded as long-term effect value for algae.

Data on the toxicity of 2,4-pentanedione on the algae species *Scenedesmus quadricauda* are also available. The toxicity threshold (TT = EC_3) after a 8 d exposure period has been determined to be 2.7 mg/l (Bringmann and Kuehn 1980). As there is no information whether the algae were in the exponential growth phase during the whole test, these data cannot be used for the effects assessment.

In semi-static long-term studies the effect of 2,4-pentanedione on the reproduction rate of *Daphnia magna, Daphnia pulex* and *Ceriodaphnia reticulata* was investigated. For reproductive impairment the determined LOEL- (EC_{16}), MATC- (maximum acceptable toxicant concentration: geometric mean between the highest test concentration with no significant effect and the next highest concentration with a significant effect) and chronic EC_{50}-values in *D. magna* were 0.5, 6.5 and 6.5 mg/l (95 % C.I. = 5-9 mg/l), respectively, after a 14 d exposure time. For *D. pulex* the corresponding MATC and chronic EC_{50}-values were determined to be < 0.87 mg/l and 1.0 mg/l (95 % C.I. = 0.2 - 1.7 mg/l), respectively (Elnabarawy et al. 1986). For *Ceriodaphnia reticulata* after a 7d exposure time a MATC of < 0.87 mg/l and a EC_{50} of 2.6 mg/l was found. For both *Daphnia pulex* and *Ceriodaphnia reticulata* significant effects on reproduction were found at the lowest test concentration of 0.87 mg/l. No NOEC can be derived for these species. For *Daphnia magna* a LOEL (EC_{16}) of 0.5 mg/l was found. According to the EU Technical Guidance Documents a NOEC can be derived from this value by dividing it by a factor of 2, as the effects were between 10 and 20 %. Therefore, the NOEC for *Daphnia magna* is determined to 0.25 mg/l.

A high acute/chronic ratio was found for Daphnia magna (about 100). As 2,4-pentanedione is known to be a nerve toxin, it is possible that also for fish the acute/chronic ratio is high. However, no long-term fish test is available to confirm this assumption.

For the derivation of the $PNEC_{aqua}$ the NOEC of 0.25 mg/l found for *Daphnia magna* is used as basic value. As long-term tests with species representing two trophic levels are available (daphnids and green algae), an assessment factor of 50 is proposed.

Therefore: PNECaqua = 0.25 mg/l / 50 = 0.005 mg/l

As the basic Daphnia study was performed over a period of only 14 days without analytical monitoring, it cannot be excluded that a NOEC from a 21d test with analytical monitoring is lower. Therefore, the above derived PNEC has to be regarded as tentative.

4.2 Terrestrial Effects

No data available as to the effects of 2,4-pentanedione on terrestrial organisms.

4.3 Other Environmental Effects

In the cell multiplication inhibition test the effect of 2,4-pentanedione on microorganisms was studied. In the bacterial strain *Pseudomonas putida* the toxicity threshold (TT = EC_3) after a 16 h exposure period has been determined to be 67 mg/l indicating only slight to moderate toxicity in this specific bacterial strain. In the same investigation the flagellate protozoa *Entosiphon sulcatum* proved to be more sensitive as demonstrated by the determined toxicity threshold (TT = EC_3) of 11 mg/l after a 72 h exposure period (Bringmann and Kuehn 1980).

The toxicity of 2,4-pentanedione was tested in the early embryo growth and sperm cell toxicity test, respectively, using the sea urchin (*Arbacia punctulata*) as a representative of a marine species. EC_{50}-values obtained were 105.4 mg/l (early embryo growth test, overall exposure four hours) and 0.9 mg/l (sperm cell toxicity test, one hour exposure period), respectively (Nacci et al. 1986).

4.4 Initial Assessment for the Environment

Due to its high water solubility and considering its vapour pressure 2,4-pentanedione is mainly released to the aqueous environment (about 90 %) and only a minor portion to air (about 10 %) on the basis of a Mackay level I calculation. Based on a calculation according to Atkinson the substance is being degraded in the atmosphere by photochemically produced hydroxyl radicals with a half life of 14 days. Due to its chemical structure the material does not undergo hydrolysis in water. 2,4-Pentanedione is readily biodegradable and on the basis of the determined n-octanol/water-partition coefficient the substance shows no potential for bio- and geoaccumulation.

In the aqueous compartment the acute toxicity of 2,4-pentanedione has been tested in the three trophic levels fish, water flea and algae, respectively. The lowest effect values found were:

Lepomis macrochirus: 96h-LC_{50} = 60.1 mg/l

Daphnia magna: 48h-EC_{50} = 34.4 mg/l

Scenedesmus sp.: 24h-IC_{10} = 100 mg/l; 24h-IC_{50} > 300 mg/l

On the basis of the results obtained the material has to be considered as harmful to the aquatic system.

In a long-term reproduction tests with *Daphnia magna* a 14d-NOEC of 250 µg/l was derived. Applying an assessment factor of 50, a $PNEC_{aqua}$ of 5 µg/l was derived from this NOEC. As it cannot be excluded that a NOEC from a 21d test with analytical monitoring is lower, the PNEC has to be regarded as tentative.

5 RECOMMENDATIONS

Environment: The substance is a candidate for further work. As for daphnids a high acute/chronic ratio was found and the substance is known to be a nerve toxin, a high acute/chronic ratio is also assumed for fish. From product registers the use of the substance other than intermediate is evident. Therefore, an exposure assessment and if then indicated an environmental risk assessment should be performed.

Human Health: The substance is a candidate for further work. In occupational settings where exposure is not controlled and due to information of European product registers exposure to consumers and workers cannot be excluded. As the extent cannot be estimated, a human exposure assessment and, if then indicated, a risk assessment should be performed.

6 REFERENCES

Ballantyne B, Dodd DE, Myers RC, Nachreiner JJ (1986) The Acute Toxicity and Primary Irritancy of 2,4-Pentanedione. Drug Chem. Toxicol. 9: 133-146

Ballantyne B (2001) Systemic Toxicity from Repeated Cutaneous Contact with 2,4-Pentanedione. Vet. Hum. Toxicol. 9: 14-18

Bringmann G Kuehn R (1980) Comparison of the Toxicity Thresholds of Water Pollutants to Bacteria, Algae, and Protozoa in the Cell Multiplication Inhibition Test. Water Res. 14: 231-241

Bringmann G; Kuehn R (1982) Ergebnisse der Schadwirkung wassergefährdender Stoffe gegen Daphnia magna in einem weiterentwickelten standardisierten Testverfahren. Z. Wasser Abwasser Forsch. 15: 1-6

Brooke, LT, Call, DJ, Geiger, DL, Northcott, CE (1984) Acute Toxicities of Organic Chemicals to Fathead Minnows, Center for Lake Superior Environmental Studies, University of Wisconsin - Superior

Dodd DE, Garman RH, Pritts IM, Troup CM, Snellings WM, Ballantyne B (1986) 2,4-Pentanedione: 9-Day and 14-Week Vapor Inhalation Studies in Fischer-344 Rats. Fundam. Appl. Toxicol. 7: 329-339

Eastman Kodak Comp., HS&HFL No. 79-0359 (1979), USEPA New Doc. I.D. 86-920000007 (1986). Toxicity & Health Hazard Summary, Material Safety Data Sheet and Toxicity Reports on 2,4-Pentanedione with Attachments

Elnabarawy MT, Welter AN, Robideau R (1986) Relative Sensitivity of Three Daphnid Species to Selected Organic and Inorganic Chemicals. Environ. Toxicol. Chem. 5: 393-398

EPIWIN v3.05, US EPA Version July 12, 2000

Frantz SW, Ballantyne B, Leung HW (1998) Acute Intravenous and Inhalation Pharmacokinetics of 2,4-Pentanedione in the Fischer 344 Rat. Toxicol. Ind. Health 14: 413-428

Gava C, Perazzolo M, Zentilin L, Levis AG, Corain B, Bombi GG, Palumbo M, Zatta P (1989) Genotoxic Potentiality and DNA-Binding Properties of Acetylacetone, Maltol, and Their Aluminium (III) and Chromium (III) Neutral Complexes. Toxicol. Environ. Chem. 22: 149-157

HSDB (HAZARDOUS SUBSTANCES DATA BANK) search 2000

IUCLID – Existing Chemicals – 1999, Edition 1. European Commission – JRC, Environment Institute, Ispra (IT)

Krebs F (1985) Oekotoxikologische Bewertung von Abwaessern und Umweltchemikalien. Umweltforschungsplan des BMI, Forschungsvorhaben 10205115, Bundesanstalt fuer Gewaesserkunde, Koblenz

Mackay Level Fugacity Based Environmental Equilibrium Partitioning Model, Version 2.11, Trent University 1999

Mount DI, Norberg TJ (1984) A Seven Day Life-Cycle Cladoceran Toxicity Test. Environ. Toxicol. Chem. 3: 425-434

Nacci D, Jackim E, Walsh R (1986) Comparative Evaluation of Three Rapid Marine Toxicity Tests: Sea Urchin Early Embryo Growth Test, Sea Urchin Sperm Cell Toxicity Test and

Microtox. Environmental Toxicology and Chemistry 5: 521-525

Rastogi, SC (1991) Levels of Organic Solvents in Printer´s Inks. Arch. Environm. Contam. Toxicol. 20: 543-547

RCC-CCR Test Report-No. 671200 (2000) Chromosome Aberration Assay in Mouse Spermatogonia Cells with Acetylacetone

Sterry W, Schmoll M (1985) Contact Urticaria and Dermatitis from Self-adhesive Pads. Contact Dermat. 13: 284-285

Tyl RW, Ballantyne B, Fisher LC, Tarasi DJ Dodd DE (1989) Dominant Lethal Assay of 2,4-Pentanedione Vapor in Fischer 344 Rats. Toxicol. Ind. Health 5: 463 - 477

Thurston RV, Gilfoil TA, Meyn EL, Zajdel RK, Aoki TI, Veith GD (1985) Comparative Toxicity of Ten Common Aquatic Species. Water Res. 19: 1145-1155

Union Carbide Corp. Bushy Run Research Center (1984) Project Report No. 47-132. 2,4-Pentanedione Acute and Nine Day Vapor Inhalation Study with Male and Female Rats

Union Carbide Corp. Bushy Run Research Center (1985a) Project Report No. 48-34. 2,4-Pentanedione Acute Toxicity and Primary Irritancy Studies

Union Carbide Corp. Bushy Run Research Center (1985b) Project Report No. 48-4. 2,4-Pentanedione 14-Week Inhalation Vapor Study with Rats

Union Carbide Corp. Bushy Run Research Center (1985c) Project Report No. 48-140. 2,4-Pentanedione Salmonella/Microsome (AMES) Bacterial Mutagenicity Assay

Union Carbide Corp. Bushy Run Research Center (1986a) Project Report No. 49-57. 2,4-Pentanedione Acute Exposure of Rats to Potentially Lethal Vapor Concentrations

Union Carbide Corp. Bushy Run Research Center (1986b) Project Report No. 49-20. Evaluation of the Teratogenicity of Inhaled 2,4-Pentanedione in Fischer 344 Rats

Union Carbide Corp. Bushy Run Research Center (1986c) Project Report No. 48-174. 2,4-Pentanedione In Vitro Genotoxicity Studies: CHO/HGPRT Gene Mutation Test, Sister Chromatid Assay

Union Carbide Corp. Bushy Run Research Center (1986d) Project Report No. 48-174. 2,4-Pentanedione In Vitro Genotoxicity Studies: CHO/HGPRT Gene Mutation Test, Sister Chromatid Assay

Union Carbide Corp. Bushy Run Research Center (1986e) Project Report No. 48-172. 2,4-Pentanedione In Vitro Cytogenetic Testing with Chinese Hamster Ovary Cells

Union Carbide Corp. Bushy Run Research Center (1986f) Project Report No. 49-1. 2,4-Pentanedione In Vitro Chromosome Aberration Study (Confirmatory Test)

Union Carbide Corp. Bushy Run Research Center (1986g) Project Report No. 49-124. 2,4-Pentanedione In Vivo Mouse Micronucleus Study

Union Carbide Corp. Bushy Run Research Center (1986h) Project Report No. 50-65. 2,4-Pentanedione Dominant Lethal Assay in Fischer 344 Rats by Vapor Exposure

Union Carbide Corp. Bushy Run Research Center (1990) Project Report No. 53-43. 2,4-Pentanedione Bone Marrow Chromosome Aberration Assay in Rats

Union Carbide Corp. Bushy Run Research Center (1993) Project Report No. 91U0097. 2,4-Pentanedione Bone Marrow Micronucleus Test with Swiss-Webster Mice and Sprague-Dawley-Rats

Union Carbide Corp. Bushy Run Research Center (1994a) Project Report No. 93U1254. 2,4-Pentanedione Bone Marrow Chromosomal Aberrations Assay in Mice

Union Carbide Corp. Bushy Run Research Center (1994b) Project Report No. 94U1423. 2,4-Pentanedione Bone Marrow Micronucleus Test in Rats

Union Carbide Corp. Bush Run Research Center (1995) Project Report No. 94U1378. 2,4-Pentanedione (2,4-PD) Nine-Day Repeated Cutaneous Dose Toxicity Study In New Zealand White Rabbits

I U C L I D Data Set

Existing Chemical	:	ID: 123-54-6
CAS No.	:	123-54-6
EINECS Name	:	pentane-2,4-dione
EC No.	:	204-634-0
TSCA Name	:	2,4-Pentanedione
Molecular Formula	:	C5H8O2

Producer related part

Company	:	Wacker - Chemie GmbH
Creation date	:	14.07.1993

Substance related part

Company	:	Wacker - Chemie GmbH
Creation date	:	14.07.1993
Status	:	
Memo	:	
Printing date	:	21.05.2003
Revision date	:	12.08.1993
Date of last update	:	21.05.2003
Number of pages	:	
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1. General Information **Id** 123-54-6
Date 21.05.2003

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	other: Cooperating Panel
Name	:	PDO Producers Association
Contact person	:	
Date	:	
Street	:	1250 Connecticut Avenue, N.W., Suite 700
Town	:	Washington, DC 20036
Country	:	
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

Remark	:	Cooperating Panel consists of the following companies: ---------- Union Carbide Corporation Wacker Biochem Corporation
Flag	:	Critical study for SIDS endpoint

18.07.2001

Type	:	lead organisation
Name	:	Wacker - Chemie GmbH
Contact person	:	
Date	:	
Street	:	Postfach 1260
Town	:	84480 Burghausen
Country	:	Germany
Phone	:	08677/83 4888
Telefax	:	08677/83 5590
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

Flag	:	Critical study for SIDS endpoint

06.06.2001

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

Type	:	
Name of plant	:	Wacker Chemie GmbH, Werk Burghausen
Street	:	Johannes-Hess-Str. 24
Town	:	84489 Burghausen
Country	:	Germany
Phone	:	0049 8677 83-4888
Telefax	:	0049 8677 83-5590
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

1. General Information **Id** 123-54-6
Date 21.05.2003

Flag : Critical study for SIDS endpoint
09.03.2001

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type :
Substance type : organic
Physical status : liquid
Purity : > 99.2 % w/w
Colour :
Odour :

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
04.04.2001

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

2,4-dioxopentane

Source : WACKER CHEMIE GmbH, Burghausen, Germany.

2-propanone, acetyl

Source : WACKER CHEMIE GmbH, Burghausen, Germany.

acetoacetone

Source : WACKER CHEMIE GmbH, Burghausen, Germany.

acetylacetone

Source : WACKER CHEMIE GmbH, Burghausen, Germany.

diacetylmethane

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
03.04.2001

1. General Information **Id** 123-54-6
Date 21.05.2003

1.3 IMPURITIES

Purity :
CAS-No : 7732-18-5
EC-No : 231-791-2
EINECS-Name : water
Molecular formula :
Value : = .1 % w/w

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (1) valid without restriction
Flag : confidential
04.04.2001

Purity :
CAS-No : 110-13-4
EC-No : 203-738-3
EINECS-Name : hexane-2,5-dione
Molecular formula :
Value : = .1 % w/w

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (1) valid without restriction
Flag : confidential
04.04.2001

Purity :
CAS-No : 64-19-7
EC-No : 200-580-7
EINECS-Name : acetic acid
Molecular formula :
Value : = .05 % w/w

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (1) valid without restriction
Flag : confidential
04.04.2001

Purity :
CAS-No : 108-22-5
EC-No : 203-562-7
EINECS-Name : isopropenyl acetate
Molecular formula :
Value : = .03 % w/w

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (1) valid without restriction
Flag : confidential
04.04.2001

1.4 ADDITIVES

1. General Information **Id** 123-54-6
Date 21.05.2003

1.5 TOTAL QUANTITY

Quantity : 1000 - 5000 tonnes produced in

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
03.04.2001

Quantity : 5000 - 10000 tonnes produced in

Source : Union Carbide Corporation, USA.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
06.06.2001

1.6.1 LABELLING

Labelling : as in Directive 67/548/EEC
Specific limits :
Symbols : Xn, , ,
Nota : , ,
R-Phrases : (10) Flammable
(22) Harmful if swallowed
S-Phrases : (21) When using do not smoke
(23) Do not breathe ...
(24/25) Avoid contact with skin and eyes

Country : Germany
Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
11.05.2001 (27)

Labelling : provisionally by manufacturer/importer
Specific limits :
Symbols : Xn, , ,
Nota : A, ,
R-Phrases : (10) Flammable
(20/21/22) Harmful by inhalation, in contact with skin and if swallowed
S-Phrases : (21) When using do not smoke
(23) Do not breathe ...
(24/25) Avoid contact with skin and eyes
(36/37) Wear suitable protective clothing and gloves

Country : Germany
Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
11.05.2001

1.6.2 CLASSIFICATION

Classified : as in Directive 67/548/EEC

1. General Information **Id** 123-54-6
Date 21.05.2003

Class of danger : harmful
R-Phrases : (10) Flammable
(22) Harmful if swallowed
Specific limits :

	Concentration	Classification
1st :	25 % <= C	Xn, R 22
2nd :		
3rd :		
4th :		
5th :		
6th :		
7th :		
8th :		

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
13.12.2002

Classified : provisionally by manufacturer/importer
Class of danger : harmful
R-Phrases : (10) Flammable
(20/21/22) Harmful by inhalation, in contact with skin and if swallowed
Specific limits :

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
18.07.2001

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : industrial
Category : Chemical industry: used in synthesis

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
04.04.2001

Type of use : use
Category : Intermediates

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
04.04.2001

Type of use : use
Category : Solvents

1. General Information **Id** 123-54-6
Date 21.05.2003

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
04.04.2001

Type of use : use
Category : other: co-catalyst for the polymerisation of olefins and control of curing rates in polyurethane coatings

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Flag : Critical study for SIDS endpoint
08.06.2001

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

04.04.2001

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : other: TWA 8h
Limit value : 20 ml/m3

Remark : Union Carbide Internal Exposure Standard.
Source : Union Carbide Corporation, Danbury CT, USA.
Reliability : (4) not assignable
Flag : non confidential
06.06.2001 (66)

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by : KBwS (DE)
Labelled by : KBwS (DE)
Class of danger : 1 (weakly water polluting)

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
04.04.2001 (30)

1. General Information **Id** 123-54-6
Date 21.05.2003

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

Classified by : TA-Luft (DE)
Labelled by : TA-Luft (DE)
Number : 3.1.7 (organic substances)
Class of danger :

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
04.04.2001

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

18.10.2002

Type of search : External
Chapters covered : 3, 4, 5
Date of search : 08.05.2001

Source : Wacker Chemie GmbH, Germany
18.10.2002

1.13 REVIEWS

2. Physico-Chemical Data

Id 123-54-6
Date 21.05.2003

2.1 MELTING POINT

Value : = -23 °C
Sublimation :
Method : other: no data
Year : 1998
GLP : no data
Test substance : no data

Source : Union Carbide Corporation, Danbury CT, USA.
Reliability : (4) not assignable
Data from manufacturer without proof.
Flag : Critical study for SIDS endpoint
06.06.2001 (66)

Value : = -23 °C

Reliability : (4) not assignable
Data from secondary literature
Flag : Critical study for SIDS endpoint
13.12.2002 (19)

2.2 BOILING POINT

Value : = 138 °C at

Reliability : (4) not assignable
Data from secondary literature
Flag : Critical study for SIDS endpoint
13.12.2002 (19)

Value : = 140.4 °C at 1013 hPa
Decomposition :
Method : other: no data
Year : 1998
GLP : no data
Test substance : no data

Source : Union Carbide Corporation, Danbury CT, USA.
Reliability : (4) not assignable
Data from manufacturer without proof.
Flag : Critical study for SIDS endpoint
06.06.2001 (66)

2.3 DENSITY

Type : density
Value : = .971 - .973 g/cm³ at 20 °C
Method : other: DIN 51757
Year : 1991
GLP : no data
Test substance :

2. Physico-Chemical Data **Id** 123-54-6
Date 21.05.2003

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (2) valid with restrictions
Determination according to national standard guideline.
Flag : Critical study for SIDS endpoint
18.07.2001 (44)

Type : density
Value : = .9721 g/cm³ at 25 °C
Method : other: no data
Year :
GLP : no data
Test substance : no data

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (4) not assignable
Data from secondary literature
Flag : non confidential
18.07.2001 (2)

Type : density
Value : = .9721 g/cm³ at 25 °C

Reliability : (4) not assignable
Data from secondary literature
Flag : non confidential
13.12.2002 (19)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = 3.95 hPa at 20 °C
Decomposition : no
Method : other (measured): no data
Year : 1989
GLP : no data
Test substance : no data

Remark : Original value given as 2.96 mm Hg at 20°C.
Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (4) not assignable
Data from secondary literature.
Flag : Critical study for SIDS endpoint
18.07.2001 (2)

Value : = 9.2 hPa at 20 °C
Decomposition :
Method : other (measured): no data
Year : 1998
GLP : no
Test substance : no data

Source : Wacker Chemie GmbH, Burghausen, Germany.
Reliability : (4) not assignable
National standard method without detailed documentation;

producer/manufacturer information without further proof.

Flag : Critical study for SIDS endpoint
18.07.2001 (44)

Value : = 5.53 hPa at 25 °C

Remark : Original value g iven as 4.15 mm Hg (25°C)
Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (3) invalid
The value cited in the SRC data base couldn´t be derived from the data presented in the original reference Daubert & Danner (1989)
18.07.2001 (47)

2.5 PARTITION COEFFICIENT

Partition coefficient :
Log pow : = .34 at °C
pH value :
Method : other (measured)
Year : 1986
GLP : no data
Test substance :

Source : Wacker Chemie GmbH, Burghausen, Germany.
Reliability : (4) not assignable
Secondary literature.
Flag : Critical study for SIDS endpoint
18.07.2001 (28)

Partition coefficient :
Log pow : = .4 at °C
pH value :
Method : other (measured): no data
Year : 1995
GLP : no
Test substance : no data

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (4) not assignable
Secondary literature.
Flag : Critical study for SIDS endpoint
18.07.2001 (29)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : = 16.6 vol% at 20 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description : of high solubility
Stable :
Deg. product :

2. Physico-Chemical Data **Id** 123-54-6
Date 21.05.2003

Method	:	other
Year	:	1998
GLP	:	no data
Test substance	:	
Source	:	Union Carbide Corporation, Danbury CT, USA.
Reliability	:	(4) not assignable Data from manufacturer without further proof.
Flag	:	Critical study for SIDS endpoint
24.01.2003		(66)
Solubility in	:	Water
Value	:	= 200 g/l at 20 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	of high solubility
Stable	:	
Deg. product	:	
Method	:	other: no data
Year	:	
GLP	:	no data
Test substance	:	no data
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability	:	(4) not assignable Data from manufacturer without further proof.
Flag	:	Critical study for SIDS endpoint
24.01.2003		(44)

2.6.2 SURFACE TENSION

Test type	:	other: no data
Value	:	at 20 °C
Concentration	:	
Method	:	other: no data
Year	:	
GLP	:	no data
Test substance	:	no data
Remark	:	Surface tension given as 31.2 dyn/cm.
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability	:	(4) not assignable Data from secondary literature.
Flag	:	non confidential
18.07.2001		(2)

2.7 FLASH POINT

Value	:	= 35.5 °C
Type	:	closed cup
Method	:	other: ASTM D 56
Year	:	

2. Physico-Chemical Data **Id** 123-54-6
Date 21.05.2003

GLP : no data
Test substance : no data

Source : Union Carbide Corporation, Danbury CT, USA.
Reliability : (2) valid with restrictions
National standard method without detailed documentation.
Flag : non confidential
18.07.2001 (66)

Value : = 40.5 °C
Type : open cup
Method : other: ASTM D 1310
Year :
GLP : no data
Test substance : no data

Source : Union Carbide Corporation, Danbury CT, USA.
Reliability : (2) valid with restrictions
National standard method without detailed documentation.
Flag : non confidential
18.07.2001 (66)

2.8 AUTO FLAMMABILITY

Value : = 335 °C at
Method : other: no data
Year :
GLP : no data
Test substance : no data

Source : WACKER CHEMIE GmbH, Burghaus en, Germany.
Reliability : (4) not assignable
Secondary literature.
Flag : non confidential
18.07.2001 (2)

Value : = 350 °C at
Method : other: no data
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (4) not assignable
Manufacturer data without further proof.
Flag : non confidential
18.07.2001 (44)

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

Result : other: see remark
Method : other: no data

2. Physico-Chemical Data **Id** 123-54-6
Date 21.05.2003

Year :
GLP : no data
Test substance : no data

Remark : lower explosive limit: 2.4 %/ (v/v) at 20°C
upper explosive limit: 11.4 % (v/v) at 20°C
Source : Union Carbide Corporation, Danbury CT, USA.
Reliability : (4) not assignable
manufacturer data without proof
Flag : non confidential
23.07.2001 (66)

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Conversion factor

Remark : converting factor: 1 mg/m3 = 0.240 ppm (20°C and 1,013 hPa)
Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (1) valid without restriction
Flag : non confidential
12.07.2001 (4)

Memo : acid/base constants

Remark : pKa 13.32+/-0.05 and ion-pairing constant pKNa 2.57+/-0.05 for the TS in DMSO-d6 at 25 degree C.
Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (2) valid with restrictions
Flag : non confidential
09.03.2001 (3)

Memo : solubility in organic solvents

Remark : Acetylacetone is soluble in alcohol, ether, aceton and chloroform. The material is miscible with benzene and glacial acetic acid.
Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (2) valid with restrictions
Flag : non confidential
04.04.2001 (2)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	500000 molecule/cm³
Rate constant	:	= .00000000000115 cm³/(molecule*sec)
Degradation	:	= 50 % after 14 day(s)
Deg. product	:	not measured
Method	:	other (calculated): according to Atkinson
Year	:	1989
GLP	:	no
Test substance	:	

Remark : Due to the absence of chromophoric groups acetylacetone does not undergo UV-light mediated photolysis.

Acetylacetone is removed in the atmosphere by indirect photolysis by means of photochemically produced OH-radicals.
At a concentration of 5x10e5 radicals/cm3 and a rate constant of 1.15x10e-12 cu m/moleculexsec, the atmospheric half-life of acetylacetone can be estimated to be 14 days.

Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability	:	(2) valid with restrictions Accepted calculation method.
Flag	:	Critical study for SIDS endpoint

18.07.2001 (2)

Type	:	other: calculated in water
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	6022 molecule/cm³
Rate constant	:	cm³/(molecule*sec)
Degradation	:	= 50 % after 81 day(s)
Deg. product	:	not measured
Method	:	other (calculated)
Year	:	1988
GLP	:	no
Test substance	:	other TS

Remark : The aquatic oxidation rate for acetyl acetone has been experimentally determined to be 9.9X10E9 l/mol-s at pH 6.4 (25°C).
Based on this rate and a hydroxyl radical concentration of 1X10E-17 mol/l in water under continuous sunlight, the half-life for the aquatic oxidation of acetyl acetone can be estimated to be 81 days.

Note:
---
1) a hydroxyl radical concentration of 1x10exp-17mol/l corresponds to 6022 hydroxyl radicals/cm3 taking into account Avogadro´s constant.

Source : WACKER CHEMIE GmbH, Burghausen, Germany.

3. Environmental Fate and Pathways **Id** 123-54-6
Date 21.05.2003

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles.
Flag : Critical study for SIDS endpoint
01.08.2001 (16)

3.1.2 STABILITY IN WATER

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C

Remark : Acetylacetone does not contain any structural units prone to hydrolysis. In general, ketones are resistant to hydrolysis. Consequently, hydrolysis is not a relevant environmental removal process for acetylacetone.
Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (1) valid without restriction
Known property of this class of substances.
Flag : Critical study for SIDS endpoint
18.07.2001 (1)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : adsorption
Media : water - soil
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other
Year : 1997

Remark : The water solubility of acetylacetone has been determined to be 166 - 200 g/L at 20°C. In addition with a (measured) partition coefficient of 0.4, soil adsorption constants were estimated to be in the range of 6 - 28 indicating high mobility of acetylacetone in soil.
Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (4) not assignable
Data taken from secondary literature.
Flag : Critical study for SIDS endpoint
11.05.2001 (1)

Type : volatility
Media : soil - air

3. Environmental Fate and Pathways **Id** 123-54-6
Date 21.05.2003

Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method :
Year :

Remark : Considering the vapour pressure of approx. 9 hPa, volatilization from dry surfaces into the atmosphere cannot be excluded.
Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (4) not assignable
Assumption made on the basis of physical chemical properties.
Flag : non confidential
18.07.2001

Type : volatility
Media : water - air
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other
Year : 1997

Remark : Based on a water solubility of 166 g/L and a vapour pressure of 9.2 hPa, a Henry's law constant of 0.555 Paxm3/mol can be calculated for acetylacetone, indicating a slow volatilization from aqueous media.
Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (2) valid with restrictions
Based on an accepted calculation method (H=vp/wsol) using given physicochemical parameters.
Flag : Critical study for SIDS endpoint
21.05.2003 (1)

Type : volatility
Media : water - air
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method :
Year :

Remark : The half-lives for volatilization from model rivers (1 m deep) and model environmental pond have been estimated to be 15 and 170 days, respectively.
Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability : (4) not assignable
Data taken from secondary literature.
Flag : non confidential
18.07.2001 (2)

Type : fugacity model level I
Media : other: air-water-soil-sediment-biota
Air : 10.05 % (Fugacity Model Level I)
Water : 89.77 % (Fugacity Model Level I)

Soil	:	.17 % (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	other: Calculation according to Mackay
Year	:	2000
Remark	:	Input parameter: log Kow :0.34 water solubility: 166 g/l vapor pressure : 920 Pa melting point : - 23 °C
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability	:	(2) valid with restrictions Accepted calculation method.
Flag	:	Critical study for SIDS endpoint

27.01.2003

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	activated sludge
Concentration	:	100 mg/l related to Test substance related to
Contact time	:	
Degradation	:	= 79 - 88 (±) % after 28 day(s)
Result	:	readily biodegradable
Deg. product	:	
Method	:	OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year	:	
GLP	:	no data
Test substance	:	no data
Remark	:	The test was conducted in accordance with "Biodegradation test of chemical substance by microorganisms etc." stipulated in the Order Prescribing the Items of the Test Relating to the New Chemical Substance (1974, Order of the Prime Minister, the Minister of Health and Welfare, the Minister of International Trade and Industry No. 1). This guideline corresponds to "301C, Ready Biodegradability: Modified MITI Test (I)" stipulated in the OECD Guidelines for Testing of Chemicals (1981)
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	Sludge concentration: 30 mg/l
Reliability	:	(1) valid without restriction guideline study
Flag	:	Critical study for SIDS endpoint

11.05.2001 (38)

3.6 BOD5, COD OR BOD5/COD RATIO

BOD5

3. Environmental Fate and Pathways **Id** 123-54-6
Date 21.05.2003

Method	:	other
Year	:	
Concentration	:	related to
BOD5	:	mg/l
GLP	:	
COD		
Method	:	other
Year	:	
COD	:	= 1787 mg/g substance
GLP	:	
Remark	:	COD determined by the dichromate methode; inoculum at BOD5 bacterial strains from domestic sewage.
Result	:	ThOD for 1 g TS 1920 mg O2; 93.1% degradation at COD measurement; BOD5: 1340 mg O2/g, 70% degradation (BOD related to ThOD).
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test substance	:	no data
Reliability	:	(2) valid with restrictions Internal report of WACKER Chemie without methodology cited.
Flag	:	non confidential

18.07.2001 (69)

3.7 BIOACCUMULATION

BCF	:	= 3.16
Elimination	:	
Method	:	other: calculated
Year	:	2000
GLP	:	no
Test substance	:	no data
Remark	:	LogKow used: 0.40 logBCF: 0.5 Log BCF was calculated with the program EPIWIN. For nonionic substances with a log Kow < 1.0 this program specifies a log BCF = 0.5, which is in accordance with recommendations of the US EPA.
Source	:	Wacker Chemie GmbH, Burghausen, Germany.
Reliability	:	(2) valid with restrictions Bioaccumulation judged by accepted calculation method.
Flag	:	Critical study for SIDS endpoint

21.05.2003

3.8 ADDITIONAL REMARKS

4. Ecotoxicity **Id** 123-54-6
Date 21.05.2003

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	flow through
Species	:	Carassius auratus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 121
95% C.I.	:	= 111 - 133
Limit test	:	
Analytical monitoring	:	yes
Method	:	other
Year	:	1985
GLP	:	no data
Test substance	:	
Remark	:	at least 5 concentrations plus control were tested; concentrations of test substance were measured by GC analysis. Statistical analysis: 95% C.I. were calculated using the Trimmed Spearman-Karber method. Regression analyses were conducted using the BMDP program.
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	temperature: 19.0°C (17.8-20.0); pH 7.72 (7.61-7.89); dissolved oxygen: 6.91 mg/l (6.51-7.77); hardness (CaCO3) 196 mg/l. fish size: 1-4g; mean fish weight: 2.49g water replacement during the tests was done every 3-8 hours. Dilution water used for tests and water in which animals were cultured prior to each test was obtained from a ground water spring source.
Test substance	:	purity > 99%
Reliability	:	(2) valid with restrictions Study well documented according to the literature reference. No study report available for further details.
Flag	:	Critical study for SIDS endpoint

19.12.2002 (48)

Type	:	flow through
Species	:	Ictalurus punctatus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 106
95% C.I.	:	= 74.1 - 151
Limit test	:	
Analytical monitoring	:	yes
Method	:	other
Year	:	1985
GLP	:	no data
Test substance	:	
Remark	:	at least 5 concentrations plus control tested; concentrations of test substance were measured by GC analysis. Statistical analysis: 95% C.I. were calculated using the Trimmed Spearman-Karber method. Regression analyses were conducted using the BMDP program.

4. Ecotoxicity **Id** 123-54-6
Date 21.05.2003

Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	temperature: 19.4°C (19.0-20.0); pH 7.81 (7.76-7.83); dissolved oxygen: 7.16 mg/l (6.95-7.62); hardness (CaCO3) 196 mg/l. fish size: 0.3-4g; mean weight: 0.63g. water replacement during the tests was done every 3-8 hours. Dilution water used for tests and water in which animals were cultured prior to each test was obtained from a ground water spring source.
Test substance	:	purity > 99%
Reliability	:	(2) valid with restrictions Study well documented according to the literature reference. No study report available for further details.
Flag	:	Critical study for SIDS endpoint
19.12.2002		(48)

Type	:	flow through
Species	:	Lepomis macrochirus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 60.1
95% C.I.	:	= 50.3 - 71.8
Limit test	:	
Analytical monitoring	:	yes
Method	:	other
Year	:	1985
GLP	:	no data
Test substance	:	
Remark	:	at least 5 concentrations plus control tested; concentrations of test substance were measured by GC analysis. Statistical analysis: 95% C.I. were calculated using the Trimmed Spearman-Karber method. Regression analyses were conducted using the BMDP program. In the second experiment conducted in bluegill the following LC50 values and 95% C.I. were determined: LC50 (96h) = 66.9 mg/l (95% C.I. = 58.4-76.6 mg/l)
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	temperature: 18.6°C (18.0-19.2) and 19.2°C (18.9-19.5); pH 7.94 (7.86-8.04) and 7.88 (7.85-7.91); dissolved oxygen: 6.19 mg/l (5.71-6.73)and 7.16 mg/l (6.89-7.39); hardness (CaCO3) 196 mg/l. fish size: 0.3-2g; mean weight: 0.47g (1st experiment) 1.89g (2nd experiment) water replacement during the tests was done every 3-8 hours. Dilution water used for tests and water in which animals were cultured prior to each test was obtained from a ground water spring source.
Test substance	:	purity > 99%
Reliability	:	(2) valid with restrictions Study well documented according to the literature reference. No study report available for further details.
Flag	:	Critical study for SIDS endpoint
19.12.2002		(48)

4. Ecotoxicity **Id** 123-54-6
Date 21.05.2003

Type	:	flow through
Species	:	Lepomis macrochirus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LLC	:	= 81
Limit test	:	
Analytical monitoring	:	yes
Method	:	other
Year	:	1990
GLP	:	no data
Test substance	:	no data
Remark	:	determination of lowest lethal concentration (LLC); ventilatory and cough frequency measured at LLC. result: ventilatory frequency significantly elevated.
Result	:	Concentration range: 29 - 201 mg/l; Hyperventilation occurred in some fish at lethal levels and, overall, ventilatory patterns displayed smooth and regular ventilation at lethal and sublethal concentrations.
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	Lake Superior water; total hardness: 40-46 mg/l (as CaCO3); alkalinity (as CaCO3): 39-42 mg/l; pH: 7.6-8.0; temperature: 20°C; continuous lighting during the test; at least 4 bluegills per concentration step were used.
Reliability	:	(3) invalid Methodological deficiencies were found.
Flag	:	Critical study for SIDS endpoint

11.05.2001 (17)

Type	:	flow through
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
NOEC	:	< 56
LC0	:	= 57
LC50	:	= 104
LC100	:	= 145
Limit test	:	no
Analytical monitoring	:	yes
Method	:	other
Year	:	1980
GLP	:	no data
Test substance	:	
Remark	:	chemical analysis by GLC.
Result	:	The number of mortalities was noted every 24 h after beginning of the test, at which time they were also removed. The estimated LC 50 with corresponding 95 % confidence interval (98,3 - 110 mg/l) was calculated using the corrected average of the analyzed tank concentrations. Mortalities (average of the duplicated tests)

control	29,2	56,6	92	148	270 mg/l
6 h	-	-	-	-	-
12 h	-	-	-	-	23
24 h	-	-	-	-	25
48 h	-	-	-	25	25

54 h	-	-	2	25	25	
72 h	-	-	3	25	25	
96 h	-	-	10	25	25	

affected fishes became hyperactive and lost equilibrium prior to death.

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition : Lake Superior water; 25.2 degree C; 6.3 mg/l dissolved oxygen; hardness 46.2 mg/l CaCO3; pH 7.37; 25 fishes per group, having a mean length of 21,8 mm and a mean weight of 0,145 g;

5 concentrations (28.5-295 mg/l) and control with duplication were tested, analytical control by GLC in 24 h intervals up to 96 h; the tank volume was 6,3 l.
Test substance : purity > 99%
Reliability : (1) valid without restriction
Study well documented meeting generally accepted principles
Flag : Critical study for SIDS endpoint
19.12.2002 (14)

Type : flow through
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 141
95% C.I. : = 113 - 175
Limit test :
Analytical monitoring : yes
Method : other
Year : 1985
GLP : no data
Test substance :

Remark : at least 5 concentrations plus control tested;
concentrations of test substance were measured by GC analysis.

Statistical analysis: 95% C.I. were calculated using the Trimmed Spearman-Karber method. Regression analyses were conducted using the BMDP program.
In the second experiment conducted in bluegill the following LC50 values and 95% C.I. were determined:

LC50 (96h) = 143 mg/l (95% C.I. = 131-157 mg/l)
Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition : temperature: 19.0°C (17.8-20.0) and 19.2°C (18.9-19.5); pH 7.72 (7.61-7.89) and 7.85 (7.75-7.91); dissolved oxygen: 6.91 mg/l (6.51-7.77)and 7.17 mg/l (6.89-7.49); hardness (CaCO3) 196 mg/l.

fish size: 0.2-1g; mean weight: 0.46g (1st experiment)
0.53g (2nd experiment)

water replacement during the tests was done every 3-8 hours.

Dilution water used for tests and water in which animals were cultured prior to each test was obtained from a ground water spring source.
Test substance : purity > 99%
Reliability : (2) valid with restrictions
Study well documented according to the literature reference.
No study report available for further details.
Flag : Critical study for SIDS endpoint

4. Ecotoxicity **Id** 123-54-6
Date 21.05.2003

18.07.2001 (48)

Type	:	flow through
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 142
Limit test	:	
Analytical monitoring	:	yes
Method	:	other
Year	:	1986
GLP	:	no data
Test substance	:	
Remark	:	result: 95% confidence limits 137-148 mg/l.
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	flow through with 99% replacement in ca. 2 h; dissolved oxygen 7.57 mg/l; pH 7.32; 43.2 mg/l CaCO3; temperature 24-26 degree C; at least 4 concentrations plus control tested in duplicate; 10 28-34 days-old fishes per group.
Test substance	:	purity > 99%
Reliability	:	(4) not assignable Reliability to be considered with restriction since literature not available yet.
Flag	:	Critical study for SIDS endpoint

12.07.2001 (68)

Type	:	flow through
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 175
Limit test	:	
Analytical monitoring	:	yes
Method	:	other
Year	:	1982
GLP	:	no data
Test substance	:	
Remark	:	chemical analysis by GLC
Result	:	The number of mortalities was noted every 24 h, starting 48 h after beginning of the test, at which time they were also removed. The estimated LC 50 was calculated using the corrected average of the analyzed tank concentrations.

Mortalities (average of the duplicated tests)

control	33,3	49,0	70,7	125	245 mg/l
48 h	-	-	-	-	7
72 h	-	-	-	-	10
96 h	-	-	-	-	10

affected fishes became hyperactive and lost equilibrium prior to death.

Test condition	:	Lake Superior water; 17.7 degree C; 7.7 mg/l dissolved oxygen; hardness 43.8 mg/l CaCO3; pH 7.35; 10 fishes per group, 60 days old, having a measured mean weight of 0.40 g; 5 concentrations (32.8 -246 mg/l) and control with duplication were tested, analytical control by GLC in 24 h intervals up to 96 h; the tank volume was

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24 l.
Test substance : purity > 99%
Reliability : (1) valid without restriction
Study well documented, meeting generally accepted principles
Flag : Critical study for SIDS endpoint
27.01.2003 (15)

Type : flow through
Species : Salmo gairdneri (Fish, estuary, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 71.7
95% C.I. : = 64.1 - 80.1
Limit test :
Analytical monitoring : yes
Method : other
Year : 1985
GLP : no data
Test substance :

Remark : at least 5 concentrations plus control tested;
concentrations of test substance were measured by GC analysis.

Statistical analysis: 95% C.I. were calculated using the Trimmed Spearman-Karber method. Regression analyses were conducted using the BMDP program.
In the second experiment conducted in trout the following LC50 values and 95% C.I. were determined:

LC50 (96h) = 92.4 mg/l (95% C.I. = 85.0 - 100 mg/l)
Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition : temperature: 10.9°C (10.4-11.9) and 10.9°C (10.3-11.6); pH 7.71 (7.62-7.92) and 7.65 (7.56-7.82); dissolved oxygen: 8.86 mg/l (8.61-9.37)and 9.22 mg/l (9.06-9.32); hardness (CaCO3) 196 mg/l.

fish size: 0.6-8g; mean weight: 0.58g (1st experiment)
1.31g (2nd experiment)

water replacement during the tests was done every 3-8 hours.

Dilution water used for tests and water in which animals were cultured prior to each test was obtained from a ground water spring source.
Test substance : purity > 99%
Reliability : (2) valid with restrictions
Study well documented according to the literature reference.
No study report available for further details.
Flag : Critical study for SIDS endpoint
29.08.2001 (48)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : = 34.4
Analytical monitoring : no

4. Ecotoxicity **Id** 123-54-6
Date 21.05.2003

Method	:	other
Year	:	1984
GLP	:	no data
Test substance	:	no data
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	closed static bioassay; animals were fed during the experiment. total hardness (CaCO3) 43-45 mg/l; pH 7.2-7.4; Lake superior water; 5 animals per concentration, age of animals < 24 hr; mortality in controls: < 20%; duplicate experiments.
Reliability	:	(2) valid with restrictions Documentation of study acceptable according to the literature reference. No study report available for further details.
Flag	:	Critical study for SIDS endpoint

18.07.2001 (39)

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	= 47.6
95% C.I.	:	= 43.4 - 52.1
Analytical monitoring	:	yes
Method	:	other
Year	:	1985
GLP	:	no data
Test substance	:	
Remark	:	method: 5 to 7 concentrations plus control were tested; concentrations of test substance were measured by GC analysis. At the end of exposure period live and dead daphniae were counted. Immobilised animals showing respiration or appendage movement were counted as live. Statistical analysis: 95% C.I. were calculated using the Trimmed Spearman-Karber method. Regression analyses were conducted using the BMDP program.
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	20 animals per group were used; age: < 24 hours; Beakers were covered with watch glasses during the test. temperature: 19.1°C (19.1-19.2); pH: 8.18 (8.05-8.27); dissolved oxygen: 7.66 mg/l (7.54-7.71); hardness (CaCO3) 196 mg/l. Dilution water used for tests and water in which animals were cultured prior to each test was obtained from a ground water spring source.
Test substance	:	purity > 99%
Reliability	:	(2) valid with restrictions Study well documented according to the literature reference. No study report available for further details.
Flag	:	Critical study for SIDS endpoint

18.07.2001 (48)

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l

4. Ecotoxicity **Id** 123-54-6
Date 21.05.2003

EC50	:	= 75
95% C.I.	:	= 72 - 78
Analytical monitoring	:	no
Method	:	other
Year	:	1986
GLP	:	no data
Test substance	:	
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	total hardness (CaCO3) 240 mg/l; pH 8.0+/-0.3; aerated (before use); carbon-filtered well water; 23 degree C; 16 h photoperiod; 10 animals per group; age: < 24 hours; at least 5 concentrations; duplicated tests; nomimal concentration; not aerated during test; mortality or immobility determined; test beakers loosely covered with watch glasses.
Test substance	:	reagent grade
Reliability	:	(2) valid with restrictions Study well documented according to the literature reference. No study report available for further details.
Flag	:	Critical study for SIDS endpoint

29.08.2001 (22)

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC0	:	= 45
EC50	:	= 100
EC100	:	= 125
Analytical monitoring	:	no
Method	:	other: immobilization test according to Bringmann & Kühn, 1977
Year	:	1977
GLP	:	no
Test substance	:	no data
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	10 animals used (age < 24 hours); medium was chlorine free tap water, saturated with oxygen; hardness 16 degree (German), pH:7.6-7.7 (not adjusted); temperature 20-22°C. test vessel was loosely covered with filter paper.
Reliability	:	(2) valid with restrictions Study well documented according to the literature reference. No study report available for further details.
Flag	:	Critical study for SIDS endpoint

18.07.2001 (11)

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC0	:	= 12
EC50	:	= 40
EC100	:	= 90
C.I. (95%)	:	= 31 - 52
Analytical monitoring	:	no
Method	:	other: immobilization test according to Bringmann & Kühn, 1982
Year	:	1982
GLP	:	no
Test substance	:	no data

4. Ecotoxicity **Id** 123-54-6
Date 21.05.2003

Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	test condition: 10 daphnids per group, age <= 24h; synthetic fresh water, saturated with oxygen, initial pH 8 +/- 0.2, temperature 20°C; nominal concentrations w ere used; beaker loosely capped with filterpaper; no solubilizing agent used.
Reliability	:	(2) valid with restrictions Study well documented according to the literature reference. No study report available for further details.
Flag	:	non confidential
18.07.2001		(8)

Type	:	static
Species	:	Daphnia pulex (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	> 48.5
Analytical monitoring	:	no
Method	:	other
Year	:	1984
GLP	:	no data
Test substance	:	no data

Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	method: closed static bioassay; animals were fed. total hardness (CaCO3) 43-45 mg/l; pH 7.2-7.4; Lake superior water; 5 animals per concentration, age of animals < 24 hr; mortality in controls: < 20%; duplicate experiments.
Reliability	:	(2) valid with restrictions Documentation of study acceptable according to the literature reference. No study report available for further details.
Flag	:	Critical study for SIDS endpoint
18.07.2001		(39)

Type	:	static
Species	:	Daphnia pulex (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	= 75
95% C.I.	:	= 72 - 78
Analytical monitoring	:	no
Method	:	other
Year	:	1986
GLP	:	no data
Test substance	:	

Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	total hardness (CaCO3) 240 mg/l; pH 8.0+/-0.3; aerated (before use); carbon-filtered well water; 2 3 degree C; 16 h photoperiod; 10 animals per group; age: < 24 hours; at least 5 concentrations; duplicated tests; nomimal concentration; not aerated; mortality or immobility determined; test beakers loosely covered with watch glasses.
Test substance	:	reagent grade
Reliability	:	(2) valid with restrictions Study well documented according to the literature reference. No study report available for further details.
Flag	:	Critical study for SIDS endpoint
18.07.2001		(22)

Type	:	static

4. Ecotoxicity **Id** 123-54-6
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Species	:	other: Ceriodaphnia reticulata
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	= 75
95% C.I	:	= 72 - 78
Analytical monitoring	:	no
Method	:	other
Year	:	1986
GLP	:	no data
Test substance	:	
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	total hardness (CaCO3) 240 mg/l; pH 8.0+/-0.3; aerated (before use); carbon-filtered well water; 23 degree C; 16 h photoperiod; 10 animals per group; age: < 24 hours; at least 5 concentrations; duplicated tests; nomimal concentration; not aerated during test; mortality or immobility determined; test beakers loosely covered with watch glasses.
Test substance	:	reagent grade
Reliability	:	(2) valid with restrictions Study well documented according to the literature reference. No study report available for further details.
Flag	:	Critical study for SIDS endpoint

27.01.2003 (22)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus quadricauda (Algae)
Endpoint	:	growth rate
Exposure period	:	8 day(s)
Unit	:	mg/l
TT	:	= 2.7
Limit test	:	
Analytical monitoring	:	no
Method	:	other: cell multiplication inhibition according to Bringmann & Kühn, 1978
Year	:	1978
GLP	:	no
Test substance	:	no data
Remark	:	TT= toxicity threshold (= EC3)
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	TS dissolved in bidistilled water; neutral pH; vials stoppered with cotton-lined metal caps; temperature: 27°C; concentrations: nominal; measurement of turbidity; vials shaken once daily;
Reliability	:	(3) invalid Study well documented according to the literature reference, but these data cannot be used for the effects assessment, because no information is provided whether the algae were in the exponential growth phase during the whole test.
Flag	:	non confidential

27.01.2003 (9) (10) (13)

Species	:	other algae: green algae, mainly Scenedesmus sp.
Endpoint	:	other: inhibition of assimilation
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC10	:	= 100
EC50	:	> 300

4. Ecotoxicity **Id** 123-54-6
Date 21.05.2003

Limit test	:	
Analytical monitoring	:	no
Method	:	other
Year	:	1985
GLP	:	no
Test substance	:	no data
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	method: static bioassay in closed system; inhibition of assimilation as endpoint; algal cultures not sterile; measurement of O2-production. temperature 20 degree C; pH not adjusted; light intensity: 3000 lx; controls incubated in darkness; 6 concentrations tested; duplicate trials.
Reliability	:	(2) valid with restrictions Documentation of study acceptable according to the literature reference. No study report available for further details.
Flag	:	Critical study for SIDS endpoint

18.07.2001 (32)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	:	aquatic
Species	:	Entosiphon sulcatum (Protozoa)
Exposure period	:	72 hour(s)
Unit	:	mg/l
TT	:	= 11
Analytical monitoring	:	no
Method	:	other: Cell Multiplication Inhibition Test according to Bringmann & Kühn 1977
Year	:	1980
GLP	:	no
Test substance	:	no data
Remark	:	TT = toxicity threshold (= EC3).
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	TS dissolved in distilled water; pH 6.9; 25°C. Cotton lined plastic caps were used; concentrations: nominal; turbidity measured as toxicity indicator;
Reliability	:	(2) valid with restrictions Study well documented according to the literature reference. No study report available for further details.
Flag	:	Critical study for SIDS endpoint

18.07.2001 (13)

Type	:	aquatic
Species	:	Pseudomonas putida (Bacteria)
Exposure period	:	16 hour(s)
Unit	:	mg/l
TT	:	= 67
Analytical monitoring	:	no
Method	:	other: Cell Multiplication Inhibition Test according to Bringmann & Kühn 1977
Year	:	1982
GLP	:	no
Test substance	:	no data
Remark	:	TT = toxicity threshold (= EC3).

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Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	TS dissolved in distilled water; pH 7.0; 25°C. Cotton lined plastic caps were used; concentrations: nominal; turbidity measured as toxicity indicator;
Reliability	:	(2) valid with restrictions Study well documented according to the literature reference. No study report available for further details.
Flag	:	Critical study for SIDS endpoint

18.07.2001 (12) (13)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Species	:	other: Ceriodaphnia reticulata
Endpoint	:	reproduction rate
Exposure period	:	7 day(s)
Unit	:	mg/l
EC50	:	= 2.6
MATC	:	< .87
Method	:	other
Year	:	1986
GLP	:	no data
Test substance	:	
Remark	:	LOEL = lowest observable effect level (EC16 = 16% reproductive impairment concentration) MATC = maximum acceptable toxicant concentration (geometric mean between highest test concentration with no significant effect and the next highest concentration with a significant effect)
Result	:	Reproductive impairment findings: --- 7d-LOEL: not determined 7d-MATC: < 0.87 mg/l 7d chronic EC50: 2.6 mg/l (95% C.I. 1.6-4.1 mg/l) Measurement of reproductive impairment was found to be a more sensitive parameter than survival for this species.
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	temperature 23°C +/- 1°C; pH 8.0+/-0.3; total hardness (as CaCO3) 240 mg/l; carbon-filtered well water (aerated before use); 16 h photoperiod/day; 10 animals per group (age < 24 hours); at least 5 TS concentrations; dissolved oxygen > 5mg/l; duplicated tests; nominal concentrations; not aerated; renewal every 2nd day; feeding every day; Individual C. reticulata were placed in 30 ml beakers containing 15 ml solution.
Reliability	:	(2) valid with restrictions Study well documented according to the literature reference. No study report available for further details.
Flag	:	Critical study for SIDS endpoint

29.08.2001 (22)

4. Ecotoxicity **Id** 123-54-6
Date 21.05.2003

Species	:	Daphnia magna (Crustacea)
Endpoint	:	reproduction rate
Exposure period	:	14 day(s)
Unit	:	mg/l
LOEC	:	= .5
EC50	:	= 6.5
MATC	:	= 6.5
Analytical monitoring	:	No
Method	:	other
Year	:	1986
GLP	:	no data
Test substance	:	
Remark	:	LOEL = lowest observable effect level ((EC16 = 16% reproductive impairment concentration) MATC = maximum acceptable toxicant concentration (geometric mean between highest test concentration with no significant effect and the next highest concentration with a significant effect)
Result	:	Reproductive impairment findings: ---------- 14d-LOEL: 0.5 mg/l 14d-MATC: 6.5 mg/l 14d chronic EC50: 6.5 mg/l (95% C.I. 5 -9 mg/l) Measurement of reproductive impairment was found to be a more sensitive parameter than survival for this species.
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Test condition	:	temperature 23°C +/- 1°C; pH 8.0+/-0.3; total hardness (as CaCO3) 240 mg/l; carbon-filtered well water (aerated before use); 16 h photoperiod/day; 10 animals per group (age < 24 hours); at least 5 TS concentrations; dissolved oxygen > 5mg/l; duplicated tests; nominal concentrations; not aerated; renewal every 2nd day; feeding every day;
Test substance	:	reagent grade
Reliability	:	(2) valid with restrictions Study well documented according to the literature reference. No study report available for further details.
Flag	:	Critical study for SIDS endpoint

29.08.2001 (22)

Species	:	Daphnia pulex (Crustacea)
Endpoint	:	reproduction rate
Exposure period	:	14 day(s)
Unit	:	mg/l
EC50	:	= 1
MATC	:	< .87
Analytical monitoring	:	no
Method	:	other
Year	:	1986
GLP	:	no data
Test substance	:	
Remark	:	LOEL = lowest observable effect level (EC16 = 16% reproductive impairment concentration) MATC = maximum acceptable toxicant concentration (geometric mean between highest test concentration with no significant effect and the next

4. Ecotoxicity **Id** 123-54-6
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highest concentration with a significant effect)

Result : Reproductive impairment findings:

14d-LOEL: not measured

14d-MATC: < 0,87 mg/l

14d chronic EC50: 1.0 mg/l (95% C.I. 0.2-1.7 mg/l)

Measurement of reproductive impairment was found to be a more sensitive parameter than survival for this species.

Source : WACKER CHEMIE GmbH, Burghausen, Germany.

Test condition : temperature 23°C +/- 1°C; pH 8.0+/-0.3; total hardness (as CaCO3) 240 mg/l; carbon-filtered well water (aerated before use); 16 h photoperiod/day; 10 animals per group (age < 24 hours); at least 5 TS concentrations; dissolved oxygen > 5mg/l; duplicated tests; nominal concentrations; not aerated; renewal every 2nd day; feeding every day;

Test substance : reagent grade

Reliability : (2) valid with restrictions
Study well documented according to the literature reference.
No study report available for further details.

Flag : Critical study for SIDS endpoint

29.08.2001 (22)

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

Memo : Marine Toxicity tests in sea urchin (Arbacia punctulata)

Remark : Test species: sea urchin (Arbacia punctulata) was used.

Three rapid marine tests were employed to investigate aquatic toxicity of acetylacetone on the sea urchin: early embryo growth test, sperm cell toxicity test and Microtox.

Results of the marine tests were compared with literature data on the toxicity of acetylacetone on fresh water fish (Pimephales promelas) and

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water flea (Daphnia magna).

Result : Comparison of test results of the two marine tests with results from standard tests in fresh water fish and water flea showed that acetylacetone was exceptionally toxic to sperm cells while sensitivity of the early embryo test was comparable to the acute toxicity tests:

Early embryo test: EC50 = 105.4 mg/l (95% C.I. 56.5-170.3)

Sperm cell toxicity test: EC50 = 0.9 mg/l (95% C.I. 0.8 -1.1)

LC50 (96hr, P. promelas) = 142.0 mg/l.

EC50 (48 hr, D. magna) = 47.6 mg/l

Source : WACKER CHEMIE GmbH, Burghausen, Germany.

Test condition : Control water preparation:
---
high salinity brine (90%) was prepared by slow, gentle heating of local seawater (Narragansett Bay, RI) to obtain salt water of acceptable quality and low bacterial content.
Dilution of brine to 30% with distilled water in the sea urchin tests.

Test samples:
---
test compound was dissolved in diluted brine. Six to ten concentrations were used for determination of toxicity in the early embryo growth and the sperm cell tests, respectively.

Test procedures:

Sea urchin embryo test: Sea urchin gametes were added to test solutions and exposed for 2h. 3 -H-thymidine was added and incorporation allowed during another 2hrs of exposure. Embryos were collected, washed and processed on filters. Incorporation of 3-H-thymidine was measured by liquid scintillation counting and EC50 and 95%-C.I. determined.

Sea urchin sperm cell test: Gametes were obtained from adults using electrical stimulation. Sperm concentrations were estimated spectrophotometrically at 540 nm after dilution to 1x10exp6 sperm/ml. Egg suspensions were counted microscopically and diluted to about 1,000/ml. Aliquots of sperm suspension (100 µl) were added to 10 ml of test solution, sperms exposed for 1 hr at 20°C and 1 ml of egg suspension was subsequently added to the test solution. Sperm:egg ratios were about 1,000:1. Fertilization (presence of fertilisation membranes) was determined by microscopic observation. Control fertilization rates were acceptable in a range of 60-90%. EC50 values and 95% C.I. were calculated by probit or moving average analyis.

Test comparison:

Results from the early embryo growth and sperm cell toxicity test were compared with LC50 (96hr) and EC50 (48hr) literature values for acetylacetone.

Reliability : (2) valid with restrictions
Documentation of study acceptable. Literature reference available.

Flag : non confidential

18.07.2001 (40)

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo	:	In vivo
Type	:	Toxicokinetics
Species	:	rat
Number of animals		
Males	:	
Females	:	
Doses		
Males	:	4,3; 43; 148.5 and 430 mg/kg bw (i.v.) and 6 h inhalation of 400 ppm
Females	:	
Vehicle	:	
Route of administration	:	other: single i.v. application and 6 h inhalation
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st.: 2nd.: 3rd.:
Toxic behaviour	:	
Deg. product	:	
Method	:	other
Year	:	1998
GLP	:	no data
Test substance	:	

Method : Intravenous study: 2,4 -pentanedione was given to four adult male Fischer 344 rats per dose by single intravenous injection of 4.3; 43; 148.5; and 430 mg/kg bw. Dosing solutions were prepared by diluting a appropriate amount of unlabeled 2,4 -pentanedione with the 14C -labeled -TS in physiological saline (0.9 %). Target radioactivity was 2 – 5 mCi. Blood was collected at appropriate intervals from a lateral tail vein until 30 hr (4.3; 43 and 148.5 mg/kg doses) or 36 hr (430 mg/kg dose group) post dosing. At 48 hr a cardiac puncture was performed for a final blood sample with all groups. Urine was collected under dry ice freezing conditions at 6, 12, 24, 36 and 48 hr and feces were collected for two 24 hr intervals post dosing. For airborne collections, room air was drawn through the metabolism cages at approximately 500 ml/min. Expired 14CO2 was trapped at 12, 24 and 48 hr post dosing. After sacrifice the carcass and the following tissues were used for radioactivity measurements: brain, heart, lungs, kidneys, perirenal fat, muscle, spleen, testes, and bone marrow. Gages were washed with deionized water and methanol (1:1).

Inhalation study: A total of fifty animals were exposed 6 hours nose-only to a target concentration of 400 ppm 14C-labeled 2,4-pentanedione, and serial groups of 3 animals were removed at the blood sampling intervals during the absorption phase. Included was a group of 4 rats which were monitored by plethysmography during exposure to ensure that there was no excessive peripheral sensory irritation with consequent changes in minute volume. Respiratory rate was measured. After exposure the animals were transferred to metabolism gages for collection of excreta over 48 hr. At the end of this period the animals were sacrificed and tissues collected prior to homogenization of the carcass. Additional 4 animals were used after the exposure phase for collection of blood samples from a lateral tail vein until 48 hr post exposure to determine plasma elimination phase

kinetics. Urine was collected at 6, 12, 24 and 48 hr post exposure, and feces for two consecutive 24 hr intervals. Volatiles and expired 14CO2 were collected at 6, 12, 24 and 48 hr. Gages and heads of the animals were washed with deionized water and methanol (1:1).

Pharmacokinetic description of plasma 14C disposition following intravenous application was derived using RSTRIP, a pharmacokinetic curve-stripping and -fitting program.

Result : Intravenous study: After a single intravenous injection the plasma concentration of 14C-labeled-TS derived radioactivity declined in a biexponential fashion, with a rapid initial phase followed by a slower terminal phase. The pharmacokinetic parameters derived were: initial elimination rate constants (k alpha (hr-1)) of 2.30; 0.97; 1.32 and 26.02; initial half-life (alpha t1/2 (hr)) of 0.30; 0.71; 0.53 and 0.03; terminal elimination constants (k beta (hr-1)) of 0.045; 0.037; 0.053 and 0.065; terminal half-life (beta t1/2 (hr)) of 15.40; 18.73; 13.08 and 10.66; maximum plasma concentrations (Cmax (µg/g)) of 16.13; 110.8; 499.40 and 4369.46; apparent volumes of distribution (Vd (l/kg)) of 1.79; 2.49; 1.28 and 0.78, mean residence time (MRT (hr)) of 12.8; 12.1; 10.3 and 10.5; and areas under the curve to infinity (AUC (µg hr/g)) of 53.28; 467.09; 2196.61 and 8505.12 for the 4.3; 43; 148.5 and 430 mg/kg doses, respectively.
The overall form of the 14C plasma concentration-time curves and derived pharmacokinetic parameters indicated that dose-linear kinetics occurred in the dose range of 4.3 - 148.5 mg/kg, but not with 433 mg/kg. Metabolism of 2,4-pentanedione was quite rapid as the concentration of unmetabolized TS declined steadily to undetectable after 8 hr in the 430 mg/kg dose group. 14C-TS derived radioactivity was eliminated mainly as 14CO2 and in urine. For the 4.3; 43 and 148.5 mg/kg doses 14CO2 elimination was relatively constant (36.8; 38.8 and 42.3 % in 48 hr samples, respectively) and greater than urinary excretion (17.9; 14.3 and 29.6 % in 48 hr samples, respectively). At 430 mg/kg there was a reversal of the excretion pattern, with urine 14C excretion (54.7 %) becoming greater than that for 14CO2 (27.3 %). Excretion in expired volatiles and feaces was small.
Radiochromatograms of urine showed free 2,4-pentanedione in the 12 hr sample, together with 7 other metabolites. Most of the urinary radiolable was excreted within the first 24 hr post dosing. Unmetabolized 2,4-pentanedione and 6 of the metabolites decreased or were not detectable in the 24 or 48 hr urine samples, but one peak was still detectable in this samples. Carcass radioactivity ranged from 5.32 to 9.07 %. Total recovery ranged from 69.0 % at the 4.3 mg/kg dose to 95.18 % at the 430 mg/kg dose.

Inhalation study: Nose-only exposure to 400 ppm 14C-labeled 2,4-pentanedione produced mean decrease in breathing rate of 20.1 %, which was constant and sustained throughout exposure, due to a lengthening of the expiratory phase of the respiratory cycle, and therefore suggesting a peripheral sensory irritant effect. 14C-2,4-pentanedione was rapidly absorbed during the first 3 hr of exposure, than began to plateau, but did not reach a steady state. Postexposure elimination of 14 C from plasma followed a biphasic pattern, which was quantitatively similar to that for the intravenous studies. The pharmacokinetic parameters derived were: initial elimination rate constants (k alpha (hr-1)) of 0.162; initial half-life (alpha t1/2 (hr)) of 4.26; terminal elimination constants (k beta (hr-1)) of 0.023; terminal half-life (beta t1/2 (hr)) of 30.72; mean residence time (MRT (hr)) of 13,9; and areas under the curve for the first 6 hr, for 6 hr to infinity and total (AUC (µg hr/g)) of 703.02; 2751.94 and 3454.96, respectively. Plasma unmetabolized 2,4-pentanedione was present throughout the whole of the exposure phase, but was significantly less than total 14C. Post exposure, plasma unmetabolized TS declined rapidly to undetectable concentrations

by 12 hr. 14C excretion was approximately equivalent in urine (37.6 % over 48 hr) and expired 14CO2 (36.3 % over 48 hr), which most part of the radioactivity was eliminated in the first 12 hours. Expired volatiles, feces, tissues and carcass accounted for 2.29; 2.78; 1.66 and 17.15 % of the administered dose 48 hr post dosing, respectively. Urine radiochromatograms showed a minor 2,4 -pentanedione peak, along with 7 other peaks representing metabolites.
Immediately post exposure, radioactivity was present in all tissues examined, but on a concentration basis (µg equivalents/g) there was no preferential accumulation of 14C in any tissue or organ. On a total basis, highest contents were in liver and kidneys. By 48 hr post exposure, concentrations had decreased in all tissues except fat, presumably due to lipophilicity of 14C residues.

Reliability : (1) valid without restriction
Conduction and documentation of study very acceptable.
Literature reference available.

Flag : non confidential

16.12.2002 (23)

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Value : = 760 - 570 mg/kg bw
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 5
Vehicle :
Doses : 243, 485, 689 and 970 mg/kg bw
Method : other
Year : 1985
GLP : no data
Test substance :

Method : 5 Male and 5 female Hilltop-Wistar rats (weight 200 - 300 g) per group; 4 doses tested (0.25, 0.50, 0.71 and 1.00 ml/kg bw; equivalent to 243, 485, 689 and 970 mg/kg bw, respectively); 14 d postdosing observation period; undiluted 2,4 -pentanedione was given by means of stomach intubation with a ball-end stainless steel needle.

Remark : Original LD50 values were reported as 0.78 ml/kg bw for males and 0.59 ml/kg bw for females with 95 % confidence limits of 0.66 - 0.91 and 0.51 - 0.70 ml/kg bw, respectively.

Result : LD50 in male and female rats 760 and 570 mg/kg bw, respectively. 5/5 Males and 5/5 females died in the 1.00 ml/kg dose group and 1/5 males and 5/5 females in the 0.50 ml/kg dose group. Most deaths occurred within 5 hours after administration. Signs of toxicity at 0.50 ml/kg and higher doses included sluggishness, tremors, kyphosis, lacrimation, unsteady gait, comatose appearance and prostration. Survivors recovered at one to two days. At necropsy, findings included few remarkable lesions except enlarged cervical lymph nodes in most animals, suggesting the presence of a minor infection.

Source : Union Carbide Corporation, Danbury CT, USA.
Test substance : purity > 99 %
Reliability : (1) valid without restriction
Conduction and documentation of study very acceptable.
Literature reference and study report available.
Flag : Critical study for SIDS endpoint

5. Toxicity **Id** 123-54-6
Date 21.05.2003

13.11.2002 (6) (53)

Type	:	LD50
Value	:	= 970 mg/kg bw
Species	:	Rat
Strain	:	other: albino
Sex	:	Male
Number of animals	:	
Vehicle	:	no data
Doses	:	no data
Method	:	other: no data
Year	:	1945
GLP	:	No
Test substance	:	
Result	:	The LD50 was given as 970 (900 - 1050) mg/kg bw. Death within one day, with marked narcosis and paralysis of the respiratory center. Two other samples of 2,4-pentanedione (acid free or with high amounts of iron) killed in each case 7 of 10 rats at a dosage of 1000 mg/kg bw.
Test substance	:	2,4-pentanedione with about 6 % acetic acid
Reliability	:	(4) not assignable Essential details lacking, insufficient test compound. Study report available.
Flag	:	non confidential

13.11.2002 (36)

Type	:	LD50
Value	:	= 1050 mg/kg bw
Species	:	Rat
Strain	:	other: albino
Sex	:	Male
Number of animals	:	
Vehicle	:	no data
Doses	:	no data
Method	:	other: no data
Year	:	1941
GLP	:	No
Test substance	:	
Result	:	Death occurred within one day. Symptoms were narcosis, low body temperature, prone attitude, or coma. Deaths were apparently due to paralysis of the respiratory center. Autopsy revealed digestive tract irritation but no necrosis or erosions, and disturbed circulation as shown by congested liver and pale kidneys.
Test substance	:	2,4-pentanedione, purity not indicated
Reliability	:	(4) not assignable Essential details lacking. Study report available.
Flag	:	non confidential

13.11.2002 (35)

Type	:	LD50
Value	:	= 800 mg/kg bw
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	no data
Method	:	other: no data
Year	:	1979

5. Toxicity **Id** 123-54-6
Date 21.05.2003

GLP : no data
Test substance :

Result : The LD50 was given as 800 (540 - 1184) mg/kg bw. Weakness and prostration were observed.
Test substance : 2,4-pentanedione, purity not indicated
Reliability : (4) not assignable
Essential details lacking. Study report available.
Flag : non confidential
13.11.2002 (21)

Type : LD50
Value : = 890 - 1410 mg/kg bw
Species : rat
Strain : other
Sex :
Number of animals :
Vehicle : no data
Doses : no data
Method : other: no data
Year : 1968
GLP : no
Test substance :

Remark : Single-dose peroral LD50 were determined using male Harlan-Wistar rats with normal weights (weight range 90 to 120 g) and overweight (weight > 120 g); the former were fed ad libitum until dosed while the later were fasted the night before dosing. Determined LD50 for normal weight and overweight rats were 930 (630 to 1380) mg/kg bw and 1410 (range not indicated)/kg bw, respectively (no statistically significant difference). Furthermore it is stated, that in the years 1944 to 1964 thirteen assessments of oral LD50 were run. Male Charles-River-Fischer inbred rats derived from Fischer 344 rats (CD-F) and Harlan Wistar rats were used. The LD50 determined ranged between 890 and 1450 mg/kg bw.
Test substance : 2,4-pentanedione, purity not indicated
Reliability : (4) not assignable
Essential details lacking. Study report available.
Flag : non confidential
16.12.2002 (34)

Type : LD50
Value : = 55 mg/kg bw
Species : Rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method : other
Year : 1987
GLP : no data
Test substance :

Remark : Clinical symptoms were convulsions and anesthesia (no further details given).
Test substance : 2,4-pentanedione, purity not indicated
Reliability : (4) not assignable
Essential details lacking, insufficient documentation.
Literature reference available.

5. Toxicity **Id** 123-54-6
Date 21.05.2003

Flag : non confidential
16.12.2002 (7)

Type : LD50
Value : = 951 mg/kg bw
Species : Mouse
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method : other: no data
Year : 1979
GLP : no data
Test substance :

Result : The LD50 was given as 951 (677 - 1336) mg/kg bw. Weakness and prostration were observed.
Test substance : 2,4-pentanedione, purity not indicated
Reliability : (4) not assignable
Essential details lacking. Study report available.
Flag : non confidential
16.12.2002 (21)

5.1.2 ACUTE INHALATION TOXICITY

Type : LC50
Value : = 1224 ppm
Species : Rat
Strain : Wistar
Sex : male/female
Number of animals : 5
Vehicle :
Doses : 628, 919, 1231 and 1508 ppm
Exposure time : 4 hour(s)
Method : other
Year : 1984
GLP : Yes
Test substance :

Method : Groups of 5 male and 5 female Hilltop-Wistar albino rats [HLA(WI)BR] were exposed for four hours to dynamically generated vapour of 2,4-pentanedione. Concentrations tested were 628, 919, 1231 and 1508 ppm (corresponding to 2619; 3823; 5133 and 6288 mg/m³, respectively). Chamber concentrations concurrently analysed throughout each 4-hour exposure by GC. Postexposure period 14 d; body weight determined at 0, 7 and 14 d postexposure. A static exposure was also performed for determination of LT50. Groups of 5 male and 5 female rats were exposed to 7732 and 6388 ppm (corresponding to 32242 and 26638 mg/m³) for 74 and 37 minutes (males) and 8374 and 7449 ppm (corresponding to 34920 and 31062 mg/m³ for 78 and 39 minutes (females).
Result : Dynamic exposure: The results of these tests indicate that the 4 hour dynamic LC50 (95 % confidence limits) for 2,4-pentanedione (combined male and female) is 1224 (1063 to 1409) ppm (corresponding to 5.104 (4.432 - 5.876) mg/m³). LC50 determined for combined male and female rat. Deaths were observed with both male and female rats exposed to concentrations of 1508 and 1231 ppm (mortality 8/10 and 6/10,

respectively). Deaths occurred mostly during exposure or within 24 hours post-exposure (1 exception on day 3 in male rats in the 1508 ppm group). No mortalities were observed with rats exposed to dynamic concentrations of 919 or 628 ppm. Clinical signs observed in rats of the 1508 and 1231 ppm exposure groups included periocular, perinasal and perioral wetness and encrustation, forced respiration, distended abdomen, tremors, ataxia, decreased motor activity, a negative tail and toe pinch reflex and a slow righting reflex. The respiratory difficulties decreased motor activity and ataxia persisted in survivors through post-exposure day 2. No clinical signs were observed in survivors of the 1508 and 1231 ppm exposure groups on day 6 and 5, respectively. The only clinical signs in the 919 ppm group were periocular wetness and decreased motor activity in both sexes of rats during exposure. These rats appeared normal again on post-exposure day one. In the 628 ppm exposure group, no signs of toxicity were observable during or post-exposure. Body weights were observed for all exposure groups at 14 days post-exposure; necropsy of rats that died: red lungs, dark livers, gas-filled stomachs (no effects on sacrificed survivors).

Static exposure: LT50 for male rats 52 min (average concentration 7060 ppm) and 55 min for female rats (average concentration 7912 ppm). All rats exposed to static saturated vapour died during exposure in approximately 76 minutes. No mortalities occurred for either sex at the exposure time of approximately 38 minutes. Clinical signs observed for all static exposure groups included periocular and perinasal wetness, forced respiration and hypoactivity during exposure. A negative toe and tail pinch reflex, and negative surface righting were observed in rats following the 38 minutes exposure. These animals appeared normal by post-exposure day one. No effects on body weight gains were observed by 14 days post-exposure. No gross lesions were found in survivors at necropsy. Discoloured lungs and livers were observed in rats dying during static exposure.

Source : Union Carbide Corporation, Danbury CT, USA.
Test substance : purity 99 %
Reliability : (1) valid without restriction
Conduction and documentation of study very acceptable.
Literature reference and study report available.
Flag : Critical study for SIDS endpoint
16.12.2002 (6) (64)

Type : other
Value : 1225 - 1800 ppm
Species : rat
Strain : Fischer 344
Sex : male/female
Number of animals : 10
Vehicle :
Doses : 1225 and 1800 ppm
Exposure time : 4 hour(s)
Method : other
Year : 1986
GLP : yes
Test substance :

Method : Two groups of 10 male and 10 female Fischer 344 rats were exposed to nominal 1225 or 1800 ppm (corresponding to 5108 and 7506 mg/m³, respectively) of dynamically generated vapour of 2,4-pentanedione (actual mean chamber concentrations of 1265 and 1811 ppm, respectively). 5 Male and 5 female rats were exposed to air alone for each exposure group (controls). Target concentration for the first study was 1225 ppm. This

value is the 4 -hour LC50 value for rats. Due to a lower than expected percentage of mortality, a second study with a target concentration of 1800 ppm was conducted. Animals surviving the exposure were sacrificed after a 4-day post-exposure observation period. Clinical observations, body weight determinations and microscopic examination of the brain, thymus and gross lesions were performed. Following anesthesia, survivors of the exposure were exsanguinated by severing the brachiual blood vessels and a complete necropsy was performed. Animals dying during exposure were also completely necropsied.

Remark : Background and objective: A previous inhalation study showed degenerative changes in specific brain regions and lymphoid degeneration in the thymus of rats following repeated exposure to a concentration of 650 ppm (Union Carbide Corporation Project Report No. 48-4 (1985); also cited in this dossier). The objective of this study was to assess whether similar lesions developed following a single exposure at a high (greater than or equal to the LC50 value) concentration.

Result : 2/20 (1 male and 1 female) rats died immediately following 1265 ppm exposure and 6 males and 8 females died during or within 5 hours following the 1811 ppm exposure; clinical signs were blepharospasm, lacrimation, abdominal breathing, urogenital wetness, decreased activity, encrustation around eyes and nose; survivors of 1811 ppm group with eye opacities; significantly decreased absolute body weight and body weight gain for both sexes on day 4; the only microscopic lesions related to 2,4 -pentane exposure were keratitis and thymic lymphoid atrophy in a few 1811 ppm survivors; colour changes were noted in the lungs of six male and eight female rats dying during or soon after exposure to 1811 ppm which was attributed to congestion. No degenerative lesions in the brain of rats dying from or surviving exposure to the two 2,4-pentanedione concentrations were observable.

Source : Union Carbide Corporation, Danbury CT, USA.

Test substance : purity > 99 %

Reliability : (2) valid with restrictions
Conduction and documentation of study acceptable, minor deficiencies present. Literature reference and study report available.

Flag : non confidential

16.12.2002 (24) (63)

Type : other: Inhalation Hazard Test

Value :

Species : rat

Strain : no data

Sex : no data

Number of animals :

Vehicle :

Doses :

Exposure time : 1 hour(s)

Method : other: no data

Year : 1945

GLP : no

Test substance :

Result : Exposure to vapours substantially saturated at room temperature (25°C) killed all rats. Exposure for 30 minutes killed no animals. Death was rapid and occurred during anesthesia. Autopsy revealed only slight lung irritation.

Test substance : 2,4-pentanedione, purity not indicated

Reliability : (4) not assignable
Essential details lacking. Study report available.

Flag : non confidential

16.12.2002 (36)

5. Toxicity **Id** 123-54-6
Date 21.05.2003

Type	:	other: Inhalation Hazard Test
Value	:	
Species	:	Rat
Strain	:	Sherman
Sex	:	no data
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	4 hour(s)
Method	:	other: no data
Year	:	1945
GLP	:	No
Test substance	:	
Result	:	Exposure to vapours substantially saturated at room temperature killed all of 6 rats in one hour with death occurring during exposure or shortly thereafter. Exposure for 30 minutes killed no animals. Two hour exposure to 1000 ppm killed 2/6 rats within a day and four hour exposure to 1000 ppm killed 4/6 rats within 2 hours after exposure. The inhalation of 1000 ppm resulted in aesthesia within about 2 hours with slight irritation of eyes and nose.
Test substance	:	2,4-pentanedione with about 6 % acetic acid
Reliability	:	(4) not assignable Essential details lacking. Literature reference and study report available.
Flag	:	non confidential

16.12.2002 (18) (36)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	= 790 - 1370 mg/kg bw
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male/female
Number of animals	:	
Vehicle	:	
Doses	:	9700, 4850, 1940, 970 and 485 mg/kg bw
Method	:	other
Year	:	1985
GLP	:	no data
Test substance	:	
Method	:	Undiluted 2,4-pentanedione was applied on the shaved dorsal skin (25 cm^2) of 3-5 male or female New Zealand White rabbits/group (weight 2.0 to 3.0 kg); occlusive contact for 24 h; 14 d postapplication period; 5 doses (only in males 10 and 5 ml/kg bw, equivalent to 9700 and 4850 mg/kg bw, and in males and females 2, 1 and 0.5 ml/kg bw, equivalent to 1940, 970 and 485 mg/kg bw, respectively) tested.
Remark	:	Original LD50 values were reported as 1.41 ml/kg bw for males and 0.81 ml/kg bw for females with 95 % confidence limits of 0.80-2.49 and 0.59-1.12 ml/kg bw, respectively.
Result	:	LD50 in male and female rabbits 1370 mg/kg and 790 mg/kg with 95 % confidence limits of 780 - 2420 and 570 - 1090 mg/kg bw, respectively. No animal died within the lowest dose group, but 1/5 males and 4/5 females in the 1 ml/kg dose group, 4/5 males and 5/5 females in the 2 ml/kg dose group and all males in the two highest dose groups of 5 and 10 ml/kg.

Death occurred within 1-24 h after application. Signs of toxicity at 1 ml/kg or more were: dilated pupils, salivation and at 10 ml (highest dose) convulsions; local erythema, edema and necrosis (persisted for 1 -7 d) and scab formation at day 14; no effect on body weight in survivors. Dead animals showed red mottled lungs, patchy congestion of tracheal mucosa, and a few stomachs with superficial black foci at necropsy.

Source : Union Carbide Corporation, Danbury CT, USA.
Test substance : purity > 99 %
Reliability : (1) valid without restriction
Conduction and documentation of study very acceptable.
Literature reference and study report available.
Flag : Critical study for SIDS endpoint
16.12.2002 (6) (53)

Type : LD50
Value : ca. 5 ml/kg bw
Species : rabbit
Strain : no data
Sex : no data
Number of animals :
Vehicle :
Doses : no data
Method : other: no data
Year : 1945
GLP : no
Test substance :

Remark : In the rubber dam rabbit test (no further information) with 24 contact the LD50 was close to 5 ml/kg bw. The compound was tested undiluted.
Test substance : 2,4-pentanedione with about 6 % acetic acid
Reliability : (4) not assignable
Essential details lacking. Study report available.
Flag : non confidential
13.11.2002 (36)

Type : other
Value : 10 - 20 ml/kg bw
Species : guinea pig
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : 10 and 20 ml/kg bw
Method : other: no data
Year : 1979
GLP : no data
Test substance :

Result : LD50 indicated as 10 - 20 ml/kg bw. Four guinea pigs receiving 20 ml/kg under wrap died within 24 to 72 hours of application of the test compound (no information how many animals died at 10 ml/kg bw), moderate skin irritation.
Test substance : 2,4-pentanedione, purity not indicated
Reliability : (4) not assignable
Essential details lacking. Study report available.
Flag : non confidential
16.12.2002 (21)

5. Toxicity **Id** 123-54-6
Date 21.05.2003

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	LD50
Value	:	= 807.9 mg/kg bw
Species	:	mouse
Strain	:	no data
Sex	:	male/female
Number of animals	:	5
Vehicle	:	water
Doses	:	579, 694, 833, 1000 and 1200 mg/kg bw
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other
Year	:	1986
GLP	:	yes
Test substance	:	

Method : 5 Male and 5 female mice were used per dose. The doses used were 579, 694, 8333, 1000 and 1200 mg/kg bw. Animals were observed over a period of 3 days after administration.

Result : Analysis of variance testing indicated that there was no significant difference in the mortality response for the male and female animals. Thus the LD50 was calculated using probit analysis on the combined male and female mortality values to obtain a pooled LD50 value of 807.9 mg/kg (95 % fiducial interval from 731.6 mg/kg to 889.9 mg/kg. All animals administered the 1200 mg/kg dose died within 4 hours after injection. The dose of 1000 mg/kg produced 80 % and 60 % mortality incidence and 833 mg/kg produced 60 % and 100 % mortality incidence with male and female mice, respectively.
The lowest dose to produce mortality was the 694 mg/kg dose level which produced 20 % mortality of the male and female mice. Acute clinical signs of toxicity including narcosis or lethargy were observed for all mice that survived the first few hours after dosing. Within 6 to 7 hours after injection, the animals dosed with 833 mg/kg or 1000 mg/kg had either recovered from narcosis or died. The animals that recovered appeared ataxic, exhibited splayed hind quarters, body tremors and lacked a righting reflex when dropped from a high of 6 inches. No significant effects on body weights were observed.

Source : Union Carbide Corporation, Danbury CT, USA.

Test substance : purity 99.2 %

Reliability : (2) valid with restrictions
Conduction and documentation of study very acceptable. Study report available.

Flag : non confidential

16.12.2002 (65)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	.5 undiluted
Exposure	:	Occlusive
Exposure time	:	4 hour(s)
Number of animals	:	6
Vehicle	:	
PDII	:	
Result	:	slightly irritating

5. Toxicity **Id** 123-54-6
Date 21.05.2003

Classification	:	not irritating
Method	:	Draize Test
Year	:	1985
GLP	:	no data
Test substance	:	
Method	:	0.5 ml undiluted 2,4-pentanedione were applied to the clipped, intact dorsal skin of 6 New Zealand White rabbits (3 males and 3 females) under a gauze patch and were loosely covered with impervious sheeting. Skin reaction was scored by the method of Draize at 1 hour and 1, 2, 3, 7 and 14 days after removal of the dressing.
Result	:	One hour after removal of the occlusive dressing slight erythema detectable in 5/6 animals (average score 0.8); after 24 hours erythema detectable in 6/6 animals (average score 1.0); moderate edema formation observable in 1/6 rabbits and slight edema formation in 5/6 rabbits one hour after removal of the occlusive dressing (average score 1.2); after 24 hours slight edema still present in 5/6 rabbits (average score 0.8). After 48 and 72 hours five and three animals revealed just detectable erythema, respectively (average scores 0.8 and 0.5). Mild edema were observable at 48 and 72 hours in two and one animals, respectively (average scores 0.3 and 0.2). With the exception of mild desquamation no effects on day 7. Other effects were not detectable at any observation time.
Source	:	Union Carbide Corporation, Danbury CT, USA.
Test substance	:	purity > 99 %
Reliability	:	(1) valid without restriction Conduction and documentation of study very acceptable. Literature reference and study report available.
Flag	:	Critical study for SIDS endpoint
13.11.2002		(6) (53)
Species	:	rabbit
Concentration	:	other
Exposure	:	no data
Exposure time	:	3 day(s)
Number of animals	:	5
Vehicle	:	
PDII	:	
Result	:	
Classification	:	
Method	:	other
Year	:	1968
GLP	:	no
Test substance	:	
Method	:	Undiluted 2,4-pentanedione was applied in 0.01 ml amounts to the same identical spot on the clipped skin on the belly of 5 rabbits 3 times a day for 3 days. Readings were made at 24, 48 and 72 hours after initial application.
Result	:	Two different commercial samples caused nearly identical reactions. After 3 applications moderate to marked injection on 3 of 5 animals, after 6 and after 9 applications moderate to marked capillary injection on 3 animals, moderate erythma on a 4th and negative on the 5th animal.
Test substance	:	2,4-pentanedione, purity not indicated
Reliability	:	(4) not assignable Essential details lacking. Study performance with substantial deviations to the recent guidelines. Study report available.
Flag	:	non confidential
16.12.2002		(34)

Species	:	rabbit
Concentration	:	
Exposure	:	no data
Exposure time	:	
Number of animals	:	
Vehicle	:	
PDII	:	
Result	:	not irritating
Classification	:	
Method	:	other
Year	:	1968
GLP	:	no
Test substance	:	

Method	:	The rabbit belly vesicant test (no further information) was done on the abraded and intact skin of rabbits.
Result	:	Two different samples caused erythema but not edema with resulting scores of 1.88 and 1.0 (no primary irritants).
Test substance	:	2,4-pentanedione, purity not indicated
Reliability	:	(4) not assignable Essential details lacking. Study performance with substantial deviations to recent guidelines. Study report available.
Flag	:	non confidential

16.12.2002 (34)

Species	:	guinea pig
Concentration	:	undiluted
Exposure	:	Open
Exposure time	:	10 day(s)
Number of animals	:	
Vehicle	:	
PDII	:	
Result	:	moderately irritating
Classification	:	
Method	:	other
Year	:	1979
GLP	:	no data
Test substance	:	

Remark	:	Ten day repeated application to the depilated dorsum of guinea pigs (uncovered) did not exacerbate the irritative response (moderate irritation resulted from single application).
Test substance	:	2,4-pentanedione, purity not indicated
Reliability	:	(4) not assignable Essential details lacking. Study performance with substantial deviations to the recent guidelines. Study report available.
Flag	:	non confidential

13.11.2002 (21)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	
Dose	:	.1 ml
Exposure time	:	
Comment	:	

5. Toxicity **Id** 123-54-6
Date 21.05.2003

Number of animals	:	6
Vehicle	:	none
Result	:	slightly irritating
Classification	:	not irritating
Method	:	Draize Test
Year	:	1985
GLP	:	no data
Test substance	:	

Method : 6 Female New Zealand White rabbits tested. 0.1 ml of undiluted 2,4-pentanedione was instilled into the lower conjungtival sac of one eye per animal or was placed directly on the eye. The eyelids were held together for a second. The effects were scored according to Draize at one hour, approximately 6 hours, one day, 2 days, 3 days and 7 days after dosing. Fluoresœin (2 %) staining was used to determine corneal injury before dosing and at readings after one day.

Result : Results 1 h after application of the material:

Slight redness of the conjunctivae was observable in 5/6 animals (average score 0.8); slight chemosis in 2/6 and moderate chemosis in 1/6 animals (average score 0.7); slight discharge in 2/6 and moderate discharge in 3/6 animals (average score 1.3); slight inflammation of the iris in 2/6 animals (average score 0.3);

Results 4 h after application of the material:

Slight inflammation of the iris in 1/6 animals (score 0.2); slight redness of the conjunctivae in 4/6 animals (average score 0.7); slight chemosis in 2/6, moderate chemosis in 1/6 animals (average score 0.7); slight conjunctival discharge in 3/6 and moderate conjunctival discharge in 2/6 animals (average score 1.2)

24 hours post-instillation all eyes healed. Opacities of the cornea were not observable at any time.

Source	:	Union Carbide Corporation, Danbury CT, USA.
Test substance	:	purity > 99 %
Reliability	:	(1) valid without restriction Conduction and documentation of study very acceptable. Literature reference and study report available.
Flag	:	Critical study for SIDS endpoint

13.11.2002 (6) (53)

Species	:	rabbit
Concentration	:	
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	other
Year	:	1968
GLP	:	no
Test substance	:	

Remark : Two different samples were tested. 0.5 ml of both samples caused minor to moderate corneal injury in rabbit eyes. Instillation of 0.1 ml amounts resulted in no corneal injury for one sample and minor to moderate injury

for the other sample.

Test substance	:	2,4-pentanedione, purity not indicated
Reliability	:	(4) not assignable Essential details lacking. Study performance with substantial deviations to the recent guidelines. Study report available.
Flag	:	non confidential

13.11.2002 (34)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	other
Year	:	1945
GLP	:	no
Test substance	:	

Remark	:	Two different samples were tested.
Result	:	In the rabbit eye 0.001 ml produced necrosis, dense in the case of the acid sample and diffuse in the case of the acid free sample. When applied to the eye as solution in water, a 12 % solution of the acid free sample injured no eyes.
Test substance	:	2,4-pentanedione with about 6 % acetic acid or acid free
Reliability	:	(4) not assignable Study performance with substantial deviations to the recent guidelines. Study report available.
Flag	:	non confidential

16.12.2002 (36)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.5 ml
Exposure time	:	
Comment	:	no data
Number of animals	:	3
Vehicle	:	none
Result	:	slightly irritating
Classification	:	not irritating
Method	:	Directive 84/449/EEC, B.5 "Acute toxicity (eye irritation)"
Year	:	1994
GLP	:	no data
Test substance	:	

Method	:	The experiment was performed according to the EEC (1984 and 1991) and French (1984 and 1991) directives, with few modifications: ocular lesions (cornea, iris and conjunctiva) were scored (according to Draize et al., 1944) at 1 hour, then at 1, 2, 3, 4, 7 and 14 days. In the case of positive score, eyes were examined at 21 days. Any mass of material present in the conjunctival sac was removed after the 1-hour observation. Also, a fluorescein solution was used for observation of corneal lesions. Three rabbits were used per test compound, and the maximal average score (MAS) as well as score at day 1 were calculated. Raw data were used to classify chemicals according to the rating system described by Kay and Calandra (1962), and the EEC criteria.

5. Toxicity **Id** 123-54-6
Date 21.05.2003

Remark	:	Multinational interlaboratory study to investigate the bovine corneal opacity and permeability (BCOP) assay in comparison to the rabbit eye (Draize) test.
Result	:	Maximum average score (MAS): 14.0; score at day 1: 11.7; reversibility at day 4.
Test substance	:	2,4-pentanedione, purity not indicated
Reliability	:	(2) valid with restrictions Conduction and documentation of study acceptable. Literature reference available.
Flag	:	non confidential

16.12.2002 (25)

Species	:	other
Concentration	:	undiluted
Dose	:	
Exposure time	:	10 minute(s)
Comment	:	
Number of animals	:	
Vehicle	:	none
Result	:	highly irritating
Classification	:	
Method	:	other
Year	:	1994
GLP	:	no data
Test substance	:	

Method	:	Bovine corneal opacity and permeability (BCOP) in vitro assay. Bovine eyes were collected from a commercial abattoir and used within 2 hours of killing of the animals. A few laboratories used preserved corneas. 6 Corneas each in two trials were mounted in holders filled with minimum essential medium (MEM) and incubated for 1 hour at 32 °C. Thereafter the corneas were incubated with pure 2,4-pentanedione for 10 minutes. The TS was then removed and the epithelium was washed at least three times with MEM. Measurements of opacity with and without fluorescein staining were performed immediately after removing of the TS and 2 hours thereafter. Scores were calculated and the following classification system was established: score 0-25 mild irritant; 25.1-55 moderate irritant; 55.1 or higher severe irritant.
Remark	:	Multinational interlaboratory study in 12 European laboratories to investigate the bovine corneal opacity and permeability (BCOP) assay.
Result	:	The mean score from 12 laboratories was 59.8 (individual scores 34-79) and 2,4-pentanedione was classified by the authors as severe irritant.
Test substance	:	2,4-pentanedione, purity not indicated
Reliability	:	(4) not assignable Study performance with substantially deviations to the recent guidelines. Literature reference available.
Flag	:	non confidential

16.12.2002 (25)

5.3 SENSITIZATION

Type	:	Patch-Test
Species	:	human
Number of animals	:	
Vehicle	:	
Result	:	ambiguous
Classification	:	

5. Toxicity **Id** 123-54-6
Date 21.05.2003

Method	:	other
Year	:	1985
GLP	:	no data
Test substance	:	no data
Method	:	Twelve control persons were testes with 100 % test substance.
Remark	:	Gender, health status and possible allergic predispositions of test persons not specified.
Result	:	Three/12 persons showed no, 7/12 doubtful and 2/12 positive reaction to the test substance after 24 h, but not after 48 and 72 hours, respectively. The reactions observed were assessed to be possibly irritating but not sensitizing effects and it was concluded that sensitization might occur more frequently due to prolonged and close skin contact of pads containing the substance. A clear cut explanation for the observations made was not given.
Source	:	WACKER CHEMIE GmbH, Burghausen, Germany.
Reliability	:	(3) invalid Due to both the poor description of the study and the very weak irritating potential of the compound a verification of the results described is lacking. Literature reference available.
Flag	:	non confidential

16.12.2002 (46)

Type	:	other
Species	:	guinea pig
Number of animals	:	5
Vehicle	:	no data
Result	:	ambiguous
Classification	:	
Method	:	other: standardised skin sensitization test
Year	:	1979
GLP	:	no data
Test substance	:	no data
Result	:	In the reference available it is stated that 1/5 animals showed a weak response while the remaining 4/5 animals remained normal.
Reliability	:	(4) not assignable Description of study weak in the summary of a study report available.
Flag	:	non confidential

16.12.2002 (21)

5.4 REPEATED DOSE TOXICITY

Type	:	
Species	:	Rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	Inhalation
Exposure period	:	5d + 4d with a 2d non-exposure period in between (total 9d exposure)
Frequency of treatm.	:	6 hrs/day, 5 days/week
Post exposure period	:	1 d
Doses	:	0, 200, 400, 800 ppm
Control group	:	yes, concurrent vehicle
NOAEL	:	= 200 ppm
LOAEL	:	= 400 ppm
Method	:	other
Year	:	1984

5. Toxicity **Id** 123-54-6
Date 21.05.2003

GLP : Yes
Test substance :

Method : Four groups, each consisting of 10 male and 10 female Fischer F-344 rats (COBS CDF F-344/CrlBR; age at study start 51 days) were exposed (whole body) 6 hours per day/5 days per week, for 9 days to 2,4-pentanedione-vapours (9 days exposure period interrupted by a two days non-exposure period after exposure day 5); 2,4-pentanedione concentration in the exposure chamber (nominal concentrations 0, 200, 400 and 800 ppm corresponding to actual mean concentrations of 0, 197, 418 and 805 ppm, respectively) measured every 33 min during the exposure; clinical (every day prior, during and after exposure) and hematological (at sacrifice) parameters determined; body weights and organ weights (liver, heart, brain, lungs, thymus, kidneys, testes) were measured; necropsy on each rat; histopathology on high dose and control animals only; in addition histopatholgic examination of nasal turbinates in all dose groups.

Result : Mortality: No animal died.
Clinical observation: Clinical signs of irritancy (partial eyelid closure, periocular and perioral wetness) were observed in few females of the 800 ppm exposure group; no exposure-related clinical signs in other groups.
Body weights: Transient body weight loss were observed during the first week of exposure in males and females of the 800 ppm group; significantly reduced body weight gain in both sexes at 800 ppm and in male rats at 400 ppm throughout the study; no body weight alterations in the 200 ppm dose groups.
Organ weights: Due to the body weight loss in 800 ppm exposure group absolute organ weights of brain, liver, kidney and lung/bronchi were lowered. The relative weights of these organs were within or higher than control values. Absolute and relative thymus weight in males and females of 800 ppm dose group were decreased (minus 15 %, statistically significant). Also the relative thymus weight in males of 400 ppm dose group was decreased, but not statistically significant (minus 11 %). No differences in organ weights in 200 ppm dose group.
Hematology: At 800 ppm significant leucocytosis in both sexes; statistically significant increase in lymphocyte count in male rats of high dose group; significant increased mean corpuscular hemoglobin concentration and mean corpuscular hemoglobin in male rats were within the range of historical control values. By the study authors these alterations were not considered toxicologically significant because there was no effect in red blood cell count or in hemoglobin concentration. No changes in hematologic parameters were observable in animals of mid and low dose groups.
Histopathology: No treatment-related gross lesions; exposure-related inflammation of nasal mucosa, seen as multifocal areas of congestion, epithelial vacuolization, and lymphocyte or neutophile infiltration of the submucosa, in all exposed rats; necrosis of the nasal mucosa frequently in 800 ppm rats, occasionally at 400 ppm and absent at 200 ppm; mild laryngitis in 2 males rats of the 800 ppm -group. No lesions observable in the lower respiratory tract (trachea and lung). The biological significance of the mild vacuolization of the brain stem in two males of the 800 ppm group discussed by the study authors as not known.

Source : Union Carbide Corporation, Danbury CT, USA.
Test substance : purity 99.4 % at pre study analysis and 98.7 % at post study analysis
Reliability : (2) valid with restrictions
Conduction and documentation of study acceptable. Literature reference and study report available.
Flag : Critical study for SIDS endpoint
16.12.2002 (20) (64)

5. Toxicity **Id** 123-54-6
Date 21.05.2003

Type	:	
Species	:	Rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	Inhalation
Exposure period	:	14 weeks
Frequency of treatm.	:	daily 6 h, 5 days per week
Post exposure period	:	0 or 4 weeks
Doses	:	0, 100, 300, 650 ppm
Contrd group	:	yes, concurrent vehicle
NOAEL	:	= 100 ppm
LOAEL	:	= 650 ppm
Method	:	other
Year	:	1985
GLP	:	Yes
Test substance	:	

Method : 20 Male and 20 female rats (COBS CDF F-344/Crl Br) per group, with half being sacrificed at the end of exposure period and the remaining after a 4 week recovery period for the determination of the reversibility of observable effects, were exposed (whole body) to nominal concentrations of 0, 100, 300 and 650 ppm 2,4 -pentanedione, respectively. Additionally 10 male rats were added to control and high dose groups for glutaraldehyde perfusion and subsequent ultrastructural examination of sciatic nerves.

Analytical monitoring: 2,4-pentanedione concentration analysed every 33 min during the daily 6 h exposure.

Toxicity monitoring: Following parameters were determined:
clinical signs of toxicity (daily), ophtalmoscopy of the eye (prior to the first exposure and at sacrifice), neurobehavioral screening (modified Irwin screen; monthly before, during and after exposure), body weight (weekly during the study and before sacrifice), food and water consumption for 15 h in metabolic cages during the last exposure week (urincollection), organ weights (liver, kidneys, lungs, brain, heart, thymus and testes), urine chemistry (n=10 each group), serum chemistry and haematology of blood samples collected at the end of exposure or the 4-week recovery; gross pathology at termination in all groups; histopathology (nasal turbinates, larynx, trachea, lungs, epididymides, testes, spleen, thymus, urinary bladder, adrenal glands, brain (5 sections), thyroides, parathyroides, heart, kidneys, pituitary, skeletal muscle (gastronemius), sternal bone, spinal cord (lumbosacral region) and liver) in high dose, mid dose females and control group as well as brains of the mid dose group were processed for histopathology.

Result : Analytical monitoring: No decomposition or chamber loss of the metered 2,4-pentanedione; mean measured chamber concentrations were 0, 101, 307 and 650 ppm.

Toxicity results:
In the 650 ppm group all females and 10/30 male rats died between the 2nd and 6th week. Rats of this dose group had severe clinical abnormalities (e.g. lacrimation, ataxia, hypoactivity, hypothermia, encrustation in the perioral, perinasal abd periocular areas, incoordination, paresis).
Survivors of the 650 ppm group had decreased body weight gains, decreased absolute organ weights, but increased relative organ weights, and minor alterations in haematology (reduced hematocrit and hemoglobin and volume, increased lymphocytes), serum chemistry (increase in urea

nitrogen and alkaline phosphatase activity, decrease in creatinine, calcium, and aspartate aminotransferase (AST) activity), and urinary chemistry (low pH (6.0 vs 7.0 in controls), slightly increased bilirubin and urobilinogen). Noteworthy lesions in animals that died after exposure to 650 ppm were acute degenerations in the deep cerebellar nuclei, vestibular nuclei and corpora striata and acute lymphoid degenerations in the thymus. Many of the male survivors in this group (7/15, non-recovery and recovery group combined; all females of this dose group had died) had gliosis and malacia in the same brain regions but no peripheral neuropathy, minimal squamous metaplasia in the nasal mucosa, and lymphocytosis. Most of the rats with microscopic findings in the brain show deficits abnormal midair righting reflex, impaired gait) during the Irwin neurobehavioral screen after one month of exposure.
The majority of rats that survived the first month of exposure to 650 ppm did not exhibit neurobehavioral signs. No degenerative changes were seen in the spinal cords and ultrastructural microscopic evaluation of sciatic nerves did not produce any evidence of a peripheral neuropathy.
Most of the observed alterations in male rats of the 650 ppm group that survived the 14 weeks exposure regimen decreased in frequency and/or severity after the 4 weeks recovery period. Additionally there were no treatment related neurobehavioral signs of abnormality in rats examined following the 4-week recovery period.

There were no substance related mortalities in the 300, 100 and 0 ppm groups. Also there was no evidence of clinical signs (including Irwin neurobehavioral screen) or histologic lesions in these rats. However, females of the 300 ppm group had slightly decreased body weight gains (final body weight 5 % lower than controls) and in both sexes minor concentration related alterations in hematology, serum and urine chemistry were observed. Furthermore, these changes were completely reversible following a 4 weeks recovery period.

In the 100 ppm group no differences from controls were detectable.

In all surviving males the mean testes weights and testes weights expressed as % of organ weight determined on necropsy right at the end of the study were not different from controls in any treatment group. The same observation was made for animals of the recovery group. No histopathological changes were noted in the testes and epididymis in any dose group of surviving males examined immediately after study termination and after a 4 week recovery period, respectively. One/10 control animals of the recovery group was diagnosed with epididymitis.

In male animals of the high dose group which died during exposure atrophy of the seminal vesicles were seen in four males and degeneration of the seminiferous tubules in two animals.

In the female rats uterus, cervix and ovaries were subject to histopathological examination. No pathological findings were observable after gross and microscopical examination of uterus, cervix and ovaries in any treatment group immediately after study termination. In females of the recovery group ovarial cysts ("cystic ovarian bursa") were found in 2/10 animals of the control group but none in the treated groups. One/10 animals each of the control and intermediate dose group had changes in uterus size ("luminal ectasia") while 1/10 animals of the intermediate dose group had size changes in the cervix ("luminal ectasia").

In conclusion, the results of this study would support 100 ppm as the NOAEL, 300 ppm as the LOEL and 650 ppm as the LOAEL based on the

reversibility of effects seen in the 300 ppm dose group.

Source : Union Carbide Corporation, Danbury CT, USA.
Test substance : purity=99%
Reliability : (1) valid without restriction
Conduction and documentation of study acceptable. Literature reference and study report available.
Flag : Critical study for SIDS endpoint
16.12.2002 (20) (24) (58)

Type :
Species : rat
Sex : no data
Strain : no data
Route of admin. : gavage
Exposure period : 1-15 days, 1-11 applications
Frequency of treatm. : once daily
Post exposure period : no
Doses : 0, 100, 500, 1000 mg/kg bw
Control group : yes, concurrent vehicle
Method : other
Year : 1979
GLP : no data
Test substance : no data

Method : First experiment: 5 Rats per dose group revived 0, 100, 500, or 1000 mg/kg bw of 2,4-pentanedione by gavage once a day. The doses were administered 1 to 11 times over a 1-15 day period. Controls received distilled water. In the 100 mg/kg dose group a 11th (lethal) dose of 1000 mg/kg was given.
Second experiment: An additional group of 5 male rats received 100 mg/kg of 2,4-pentanedione ten times over a 14 d period. 5 male control animals received 100 mg/kg of distilled water.

Result : First experiment: 1000 mg/kg: rapid onset of dyspnea and depression followed by prostration and death of all rats within 1 h after first dosing; no 2,4-pentanedione related changes at autopsy.
500 mg/kg: like high dose rats except that tremors and ataxia were observed; 3/5 rats died and 2/5 were sacrificed due to poor condition after 4 applications; autopsy: 2/5 rats with poor haircoats, 1/5 distended bladder, congested lungs, clouding of cornea; histopathology: thymic necrosis (4/5), hepatocytes swelling and hepatic congestion (3/5), nephrosis (1/5), lymphadenitis of mesenteric lymph nodes (2/5), inflammation of the heart (3/5).
100 mg/kg: slight depression after applications (persisted 24 h in one rat which developed head tilt to the left side); all rats died after the final application of 1000 mg/kg or were sacrificed in moribund state; histopathologically no 2,4-pentanedione related changes.
Second experiment: no differences between the 100 mg/kg dose group and the control group with regard to clinical signs, weight gain, hematology, clinical chemistry, organ weights, gross pathology and histopathology.

Reliability : (2) valid with restrictions
Conduction and documentation of study acceptable. Summary of study report available.
Flag : Critical study for SIDS endpoint
16.12.2002 (21)

Type :
Species : rat
Sex : male
Strain : no data

5. Toxicity **Id** 123-54-6
Date 21.05.2003

Route of admin.	:	gavage
Exposure period	:	
Frequency of treatm.	:	
Post exposure period	:	
Doses	:	100 to 250 mg/kg bw
Control group	:	
Method	:	other
Year	:	1979
GLP	:	no data
Test substance	:	
Remark	:	10 rats in total received varying doses of 100 to 250 mg 2,4-pentanedione/kg bw. The exposure ranged from a few days to as many as 81 over 126 days. This resulted in deaths, weakness, ataxia, tremors, shuffling gait, head tilt, increased respiratory rate, depression, increased muscle tone, abnormal positioning of the limbs; changes seen at autopsy included poor general condition, gastric hemorrhage, gastric ulceration, and healed gastric ulcer; histologic changes included inflammatory changes of the mucosal stomach surface, necrosis of the cortical lymphocytes in the thymus and thymic atrophy, perivascular edema, hemorrhage into the Virchow-Robbin spaces and endothelial cell swelling in the brainstem and cerbellum.
Test substance	:	2,4-pentanedione, purity not indicated
Reliability	:	(4) not assignable Study performance and documentation insufficient with substantially deviations to the recent guidelines. Study report available.
Flag	:	non confidential

16.12.2002 (21)

Type	:	
Species	:	rabbit
Sex	:	male
Strain	:	New Zealand white
Route of admin.	:	gavage
Exposure period	:	two weeks
Frequency of treatm.	:	5 days per week
Post exposure period	:	no
Doses	:	250, 500 and 1000 mg/kg bw
Control group	:	
Method	:	
Year	:	1979
GLP	:	no
Test substance	:	
Method	:	Groups of two male New Zealand rabbits per dose level received daily doses of 250, 500, and 1000 mg/kg bw 5 days/week, two weeks.
Result	:	1000 mg/kg bw: Both rabbits died within 24 hours after receiving the first dose. The rabbits showed at autopsy congestion of the brain, lungs and thymus, and histologically congestion and hemorrhage in th e thymus. 500 mg/kg bw: One rabbit died on the ninth day of the study and the other on the twelfth day following severe central nervous system depression. Gross changes included hemorrhage in the brain, an atrophic thymus, pulmonary congestion, and gastric mucosal hemorrhages into the mediastial fat, marked thymis atrophy with heavy macrophage infiltration, and gastric mucosal hemorhage. 250 mg/kg bw: One of the two rabbits died on the fourth study day due to an acute necrotizing bronchopneumonia which may have been due to aspiration of the test compound. The other rabbit survived until study day 14. The animal showed no compound related cross lesions and also no

histogic lesions.

Test substance	:	2,4-pentanedione, purity not indicated
Reliability	:	(4) not assignable Study performance and documentation insufficient with substantially deviations to the recent guidelines. Study report available.
Flag	:	non confidential

16.12.2002 (21)

Type	:	
Species	:	Rabbit
Sex	:	male/female
Strain	:	New Zealand white
Route of admin.	:	Dermal
Exposure period	:	9 days
Frequency of treatm.	:	5 days first week, 4 days second week
Post exposure period	:	4 week recovery period
Doses	:	0.25, 1.0, 1.5 ml/kg bw
Control group	:	yes, concurrent vehicle
NOAEL	:	244 mg/kg bw
LOAEL	:	975 mg/kg bw
Method	:	other
Year	:	1995
GLP	:	yes
Test substance	:	

Method	:	New Zealand White rabbits were treated by 6 h occluded cutaneous application with undiluted 2,4-pentanedione at dose volumes of 0.25, 1.0 and 1.5 ml/kg body weight. Animals in the control group received occluded applications of Milli-Q filtered water at a volume of 1.5 ml/kg bw. The test or control substance was applied to the clipped dorsal surface of the rabbits. Twelve animals/sex/group were used for the control and high dose groups, 6 animals/sex/group for mid and low dose groups. The original study design included dosing for 5 days the first week and 4 day the second week. The additional 6 animals/sex/group in the controls and the high dose group were used for a 4 week recovery period. Due to mortality and signs of toxicity observable in mid and high dose groups, dosing was discontinued for these groups after day 4. Three surviving males and 2 surviving females from the 1463 mg/kg group were euthanized on day 4 while an additional 4 males and 3 females were retained without further dosing to day 12. Rabbits in the low dose group continued to receive a total of 9 doses (5 in the first week, 4 in the second). On day 12, 6 rabbits/sex from the control group were removed from the study since they were not required for their intended purpose as a recovery group. All other surviving rabbits were euthanized on day 12. Only 3 rabbits/sex from the control group were subjected to necropsy and histopathology. Monitors for toxicity included observations for clinical signs, including skin irritation, food consumption, water consumption, body weight and body weight change, organ weights, gross pathology and histopathology.
Remark	:	Used doses of 0.25, 1.0 and 1.5 ml/kg bw as given by the authors equivalent to 244, 975 and 1463 mg/kg bw, respectively.
Result	:	Occluded cutaneous dosing of rabbits with 2,4-pentanedione for 3 or 4 days resulted in death of 5/12 males and 7/12 females in the 1.5 ml/kg (1463 mg/kg) group and 1/6 males and 3/6 females in the 1.0 ml/kg (975 mg/kg) group. Skin irritation was observed in all dose groups. Time to onset and severity of skin irritation were generally dose-dependent and persistent in all dose groups. Signs of skin irritation included erythema, edema, desquamation/exfoliation, excoriation, fissuring, necrosis and/or ecchymosis. In the mid and high dose groups of rabbits during the first few days of the study, several signs of systemic toxicity were evident.

Numerous animals from these dose groups were hypoactive, uncoordinated and/or prostrate, had tremors, salivation, gasping and/or convulsions, and some had blue cutis of the nasal area suggestive of cyanosis. Furthermore, these groups lost mean body weight and had decreased food consumption during the first few days of the study. After cessation of dosing in these dose groups, mean food consumption generally returned to control values while mean body weight gains were increased over control values. Excessive vocalization, slow or laboured breathing, and/or red perioral discharge were also observed in some high dose group animals until cessation of dosing. In the low dose group there were no mortalities, clinical signs of systemic toxicity, or effects on body weight or food consumption. Gross and microscopic evaluation at both day 4 and 12 confirmed dose-related skin irritation in all treatment groups. Microscopic lesions included acanthosis, subcutaneous edema, dermatitis, hemorrhage, congestion and/or necrosis. There were also numerous rabbits with hemorrhaging in various sections of the brain, including the meninges. Additionally, a number of brain sections showed neuronal degeneration, including the hypothalamus, mid brain, piriform cortex, pons and/or hippocampus. At both day 4 and 12, the thymus or thymic region, spleen, and/or lymph nodes of several animals of both sexes from the mid and high dose groups were congested and/or hemorrhaged; some animals also had lymphoid depletion or necrosis. This observation, combined with decreased lymphocyte and eosinophil counts in the high dose group at day 4, suggested possible effects on the immune system. Since the animals from the mid and high dose group had severe skin irritation and many signs of systemic effects a definitive conclusion regarding a treatment related response to the immune system is not possible, as discussed by the study authors. Except clinical pathology changes that may have been related to the skin irritation, no substance related differences from controls were reported in the low dose group.

According to the systemic effects observed, 244 mg/kg bw and 975 mg/kg bw correspond to the NOAEL and LOAEL of this dermal study, respectively.

Source : Union Carbide Corporation, Danbury CT, USA.
Test substance : purity > 98 %
Reliability : (2) valid with restrictions
Conduction and documentation of study acceptable. Literature reference and study report available.
Flag : Critical study for SIDS endpoint
16.12.2002 (5) (51)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : Salmonella typhimurium, TA 98, TA100, TA1535, TA1537 and TA1538
Test concentration : 0.3 - 30 mg/plate
Cycotoxic concentr. :
Metabolic activation : with and without
Result : Negative
Method : Other
Year : 1985
GLP : Yes
Test substance :

Method : Test performed according to standard protocols by inclusion of a metabolic activation system (S9-Mix from livers of Sprague-Dawley rats pretreated

with Aroclor 1254). In preliminary trials with strain TA 100 only, a concentration of 97.4 mg/plate proved to completely inhibit bacterial growth. The next lower concentration of 30 mg/plate showed some toxic effects. Accordingly, doses selected on the basis of these trials were 0.3, 1.0, 3.0, 10.0 and 30.0 mg/plate. Incubations were run in triplicate at 37°C for 24 to 48 hours. Plates were examined for the condition of their background lawns and growth was recorded as either confluent (non-toxic), sparse (moderately toxic) or absent (toxic). The solvents of choice was water. Concurrent solvent and positive controls were run in each test. Positive control substances were without S9-mix 0.01 mg 4-nitro-o-phenylenediamine/plate for TA98 and TA1538, 0.01 mg sodium azide for TA100, 0.06 mg 9-aminoacridine/plate for TA1537 and with S9-mix 0.01 mg 2-aminoanthracene for all strains.

Result : 2,4-pentanedione did not produce a doubling or a dose-response relationship of the number of revertants/plate in the Salmonella typhimurium strains used neither in the absence nor in the presence of a metabolic activation system. Dose selection appeared to be in a suitable range, because in tests both with and without metabolic activation, bacteriotoxicty was observed at 30 mg/plate (highest dose tested) with all strains. Well proven positive controls did produce mutagenic effects demonstrating the functionality of the test system. It can therefore be concluded that 2,4-pentanedione is not mutagenic under the conditions of the assay.

Source : Union Carbide Corporation, Danbury CT, USA.

Test substance : purity 99.2 %

Reliability : (1) valid without restriction
Conduction and documentation of study very acceptable. Study report available.

Flag : Critical study for SIDS endpoint

16.12.2002 (56)

Type : Sister chromatid exchange assay

System of testing : CHO cells

Test concentration : 0.02-0.1 mg/ml (without S9-Mix); 0.03-0.3 mg/ml (with S9-Mix)

Cycotoxic concentr. :

Metabolic activation : with and without

Result : Positive

Method : Other

Year : 1986

GLP : Yes

Test substance :

Method : In preliminary investigations it was shown that concentrations of 2,4-pentanedione above 2.0 mg/ml were lethal to CHO cells (CHO-K1-BH4 (subclone D1)) and a concentration of 0.3 mg/ml produced approximately a 28 % inhibition of growth when tested with an S9 metabolic activation system and a 38 % inhibition of growth in tests without S9-mix. For the main test the maximum concentrations chosen were 0.1 and 0.3 mg/ml in the absence and presence of a metabolic activation system, respectively. Cells were incubated in duplicate with at least 5 dose levels and SCE production was determined for the three highest doses which did not produce excessive cytoxic inhibition of cell division. In the absence of S9-mix 2,4-pentanedione was directly added to the culture medium and incubated for five hours. In the presence of S9-mix cells were exposed for two hours to the TS. Bromodeoxyuridine (3 µg/ml) was present in the growth medium during exposure. Metabolic activation by S9 liver homogenate, prepared from Aroclor 1254-induced, Sprague-Dawley male rats. A total of 25 cells/culture were examined for the induction of SCE. As an indicator of genotoxicity the number of SCE/cell as well as mean

number of SCE/chromosome were determined. Positive (100 µg ethylmethane sulfonate/ml without S9-mix and 300 µg dimethylnitrosamin/ml with S9-mix), negative (culture medium) and solvent controls (H2O) were included as well.

Result : A statistically significant increase in the number of SCEs was produced by the three highest doses of the TS evaluated for SCEs in the absence of a metabolic activation system. The 0.1 mg/ml dose produced a highly significant increase in the incidence of SCEs which was greater than a comparable concentration of the positive control agent EMS. 2,4-Pentanedione was therefore considered a highly active genotoxic agent in the SCE test without S9 activation.

In the presence of S9 activation a statistically significant increase in the SCE values was produced with all three doses of the test agent in comparison to the untreated controls.
The magnitude of the increase in SCEs was lower than in the test without S9 activation despite the use of a 3-fold greater amount of TS in this test. The positive increases in SCEs apparent in the test without S9 activation were also induced in the test with S9 activation. Although dose-response relationships were very steep in the test without S9-mix, and absent in the test with S9-mix, reproducible and statistically significant increases were detectable in both tests. 2,4 -Pentanedione is therefore considered genotoxic particularly in the absence of S9-mix.

Source : Union Carbide Corporation, Danbury CT, USA.
Test substance : purity 99,2 %
Reliability : (1) valid without restriction
Conduction and documentation of study very acceptable. Study report available.
Flag : Critical study for SIDS endpoint
16.12.2002 (54)

Type : other: umu-Test
System of testing : Salmonella typhimurium TA1535/pSK1002
Test concentration : 196 µg/ml without S9-mix; 410 µg/ml with S9-mix and 1234.6 µg/ml with and without S9-mix
Cycotoxic concentr. : no data
Metabolic activation : with and without
Result : Ambiguous
Method : Other
Year : 1991
GLP : no data
Test substance :

Method : The umu-test was used which detects the induction of DNA repair after incubation with genotoxic substances; beta-galactosidase activity measured as indicator for SOS-repair response; metabolic activation by S9 liver homogenate, prepared from phenobarbital and 5,6-benzoflavone-induced male rats; incubation at 37 degree C for 2-24 h.
Result : Weakly positive results with and without S9 metabolic activation after 2 h incubation at 1234.6 µg/ml; strong positive results with S9 after 24 h incubation at 410 µg/ml; negative results without metabolic activation after 2, 4, 6 and 20 h incubation at 196 µg/ml as well as with metabolic activation at 410 µg/ml; no information is given on dose-response relationship and cytotoxicity.
Test substance : 2,4-pentanedione, purity not indicated
Reliability : (2) valid with restrictions
Conduction and documentation of study acceptable. Literature reference available.
Flag : non confidential

5. Toxicity **Id** 123-54-6
Date 21.05.2003

16.12.2002 (42)

Type	:	Cytogenetic assay
System of testing	:	CHO cells
Test concentration	:	0.04-0.12 mg/ml without S9-mix; 0.06-0.14 mg/ml with S9-mix
Cycotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	Ambiguous
Method	:	Other
Year	:	1986
GLP	:	Yes
Test substance	:	

Method : Chromosomal aberration (CA) study; 2,4-pentanedione concentrations used in the test did not produce excessive cytotoxic inhibition of mitotic CHO cells (CHO-K1-BH4 (subclone D1)) as derived from preliminary investigations.
The highest three doses were selected for the determination of the incidence of chromosomal aberrations. Chromosomes were prepared by standard methods and stained using the Fluorescence plus Giemsa (FPG) technique that is used for visualization of sister chromatid exchanges. CHO cells were exposed to 2,4-pentanedione and appropriate controls for a 6 hour period in the absence of metabolic activation. Indirect genotoxic potential, requiring metabolic activation by liver S9-homogenate, was studied with a 2 hour exposure period to the TS and the S9 activation system. Following the exposure period, cells were rinsed, fresh medium was added and the cells were then harvested at 14 or 22 hours after the start of exposure for testing performed with or without activation. A total of fifty cells/culture/harvest interval was examined for chromosome damage using duplicate cultures for the test agent and controls. At least 5 dose levels were tested both with and without metabolic activation. Incidence of chromosome damage was determined for the highest 3 doses which did not produce excessive cytotoxic inhibition of cell division (mitosis). The number of chromatid and chromosome-type aberrations, the total number of aberrations per 50 cells examined (with and without including gaps in the total) and the level of statistical significance were determined. Metabolic activation by S9 liver homogenate, prepared from Aroclor 1254-induced, Sprague-Dawley male rats. Cyclophosphamide (1.5 µg/ml, with S9-mix) and triethylenamine (1.5 µg/ml, without S9-mix were used as the positive control agents to assure the reliability and sensitivity of the test system for detecting metabolic activation dependent and independent clastogens.

Remark : Cells were cultured for an additional 10 hours following the normal division time of 12 hours (2,4-pentanedione produced a significant delay in cell division cycle), thus allowing the cells a period of 22 hours to recover and complete DNA synthesis. This extended growth period enabled higher dose levels to be evaluated, and allowed the cells sufficient time to replicate DNA which is necessary for observation of synthesis-dependent types of chromosome damage. Extending the chromosome sampling period to compensate for cell cycle delays increased the sensitivity of the test system, and unequivocally demonstrated that the TS produced CAs when tested for direct clastogenic potential in CHO cells.

2,4-Pentanedione was considered by the study authors to be highly clastogenic (chromosome braking) to CHO cells in the tests performed without metabolic activation. However there are some peculiarities in the test without metabolic activation which raise doubts about the quality of the experimental performance of the study:
- It is an extremely unusual finding that a test substance produces in 98 % of the target cells chromosome aberrations at a dose level (0.03 mg/ml)

that practically does not increase the cell cycle time (increase by only 5 %) and reduces the cell number by only 34 % (data from a pre-study, measured 6 h after a 6 h treatment). Although in the present study the preparation interval was 10 h longer (16 h), a dramatic change in cell proliferation in a mass culture would not be expected within this difference of time. This is confirmed by the statement of the authors that the highest three doses which did not produce excessive cytotoxic inhibition of mitotic cells (0.03, 0.10 and 0.12 mg/ml) were scored for incidence of chromosome aberrations.
- In addition, there is no dose related increase of chromosome aberrations. This might be understandable with regard to a similar lack of a dose relationship for cytotoxicity. However, in the present study there is a dose relationship for cytotoxicity (relative cell cycle increase at 0.03; 0.06 and 0.10 mg/ml of 5, 69 and 98 %, respectively).
- Another unusual finding is, that there are very big differences in the number of aberrations per 50 cells (excluding gaps) within parallel cultures. A total of 146 aberrations is found in one sample of 50 cells while a total of only 54 aberrations is found in the cells of the parallel culture after treatment with 0.03 mg/ml. A similar discrepancy is obvious in the data of the 0.12 mg/ml treatment group (42/137).
- Furthermore, it is very strange that in heavily damaged cells with 100 % cells carrying aberrations (0.03 and 0.10 mg/ml) the number of gap-events remains in the negative control range.

Result : In tests performed without S9 activation, all three of the dose levels of 2,4-pentanedione evaluated produced significant increases in number of CAs. The proportion of cells with chromosome aberrations ranged from 95 % to 100 % in comparison to an incidence of 3 % aberrant cells for the negative control. In contrast, cells tested under more realistic physiological conditions (namely in the presence of an S9 activation system) did not show increased numbers of CA in comparison to values of control cultures. 2,4-pentanedione was considered by the study authors to be highly clastogenic (chromosome breaking) to CHO cells in tests performed without metabolic activation but it was not clastogenic when tested in the presence of a metabolic activation under the conditions of this in vitro test system.
Source : Union Carbide Corporation, Danbury CT, USA.
Test substance : Purity 99,2 %
Reliability : (2) valid with restrictions
Conduction and documentation of study very acceptable. Study report available.
Flag : Critical study for SIDS endpoint
13.01.2003 (52)

Type : HGPRT assay
System of testing : CHO cells
Test concentration : 0.005-1.5 mg/ml without S9-mix; 0.005-1.0 mg/ml with S9-mix
Cycotoxic concentr. :
Metabolic activation : with and without
Result : Negative
Method : Other
Year : 1986
GLP : Yes
Test substance :

Method : Preliminary trials were performed to determine an appropriate range of test concentration in which the highest concentrations would kill no more than (approximately) 90 % of the treated CHO cells (CHO-K1-BH4 (subclone D1)). In this preliminary experiments concentrations above 2.0 mg/ml in the presence of S9 and 3.0 mg/ml in the absence of S9 virtually killed all cells.

Doses selected for the definitive test were 0.005-1.5 mg/ml and 0.005-1.0 mg/ml in the absence and presence of S9 mix, respectively. Positive (ethylenemethanesulfonate, 200 µg/ml) and solvent (H2O) controls were included as well to determine 2,4-pentanedione related genotoxic effects as derived by the number of mutants/10e6 viable cells/dosed culture. All incubations were run in duplicate. Cells were exposed to at least five concentration which allowed sufficient cell survival for assessment of survival and quantification of mutants. Cells were exposed for 5 h in tests both with and without metabolic activation. The mutant fraction was determined after a 9 to 12 day subculturing period to allow expression of the mutant phenotype. Metabolic activation by S9 liver homogenate, prepared from Aroclor 1254-induced, Sprague-Dawley male rats.

Result : 2,4-Pentanedione did not produce any reproducible or statistically significant increases in the incidences of mutations of CHO cells at concentrations between 0.005 to 1.5 mg/ml in tests without an S9 metabolic activation system or from 0.005 to 1.0 mg/ml with S9. Random cultures with increased mutant values were within the typical range of variability for this test in the investigating laboratory and the increases were not reproducible in the duplicate cultures/dose level.
2,4-Pentanedione was not considered to be an active gene mutagen under the conditions of the CHO test system.

Source : Union Carbide Corporation, Danbury CT, USA.
Test substance : purity= 99.2%
Reliability : (1) valid without restriction
Conduction and documentation of study very acceptable. Study report available.
Flag : Critical study for SIDS endpoint
16.12.2002 (54)

Type : Cytogenetic assay
System of testing : CHO cells
Test concentration : 0.01-0.03 mg/ml without and 0.02-0.1 with metabolic activation
Cycotoxic concentr. :
Metabolic activation : with and without
Result : ambiguous
Method : other
Year : 1986
GLP : yes
Test substance :

Method : Chromosome aberration study; 2,4-pentanedione concentrations did not produce excessive cytotoxicity or inhibition of mitotic CHO cells (CHO-K1-BH4 (subclone D1)); concurrent negative (culture medium), positive (15 µg cyclophosphamide/ml with S9-mix, 1,5 µg triethylenamine/ml without S9-mix) and vehicle (solvent water) control; 2 h treatment period (cells harvested at 6 or 10 h after start of exposure) with and 6 or 10 h without metabolic activation. Chromosomes were prepared by standard methods. When possible, a total of fifty cells/culture/harvest interval was examined for chromosome damage using duplicate cultures for the test agent and controls. At least 5 dose levels were tested both with and without metabolic activation. Incidence of chromosome damage was determined for the highest 3 doses which did not produce excessive cytotoxic inhibition of cell division (mitosis). The number of chromatid and chromosome-type aberrations, the total number of aberrations per 50 cells examined (with and without including gaps in the total) and the level of statistical significance were determined. Metabolic activation by S9 liver homogenate, prepared from Aroclor 1254-induced, Sprague-Dawley male rats.

Result : Significant but small increase in aberrations (predominant simple chromatid breakages) observed at one dose level and at one sample interval in both

tests performed with and without metabolic activation. In addition to this lack of reproducibility of positive effects, no dose-related increase in aberrations was observed in the range of doses evaluated in this experiment. Because of inconsistencies in the data determined and the simple nature of lesions observed, the TS could not definitively be classified with regard to potential clastogenicity in the test with or without activation. An additional test at optimized sample intervals has been performed (BRRC Project Report No. 49-1, 1986, also cited in this dossier) to clarify the clastogenic potential of 2,4-pentanedione.

Source : Union Carbide Corporation, Danbury CT, USA.
Test substance : purity 99.2 %
Reliability : (2) valid with restrictions
Conduction and documentation of study acceptable. Study report available.
Flag : Critical study for SIDS endpoint
16.12.2002 (57)

Type : Ames test
System of testing : Salmonella typhimurium TA92, TA98, TA100 and TA 104
Test concentration : no data
Cycotoxic concentr. : no data
Metabolic activation : without
Result : ambiguous
Method : other: according to the protocol originally described by Bruce Ames et al. (1975)
Year : 1989
GLP : no data
Test substance :

Method : The total volume of the plates was 22 ml, including 20 ml of culture medium and approximately 2 ml of top agar; it was reported that the test chemicals were applied as aqueous solutions or in DMSO at a final volume of 0.1 ml. It is not clear from the publication what solvent was used for 2,4-pentanedione. No metabolic activation system (e.g. liver S9 mix) was included.

Water or DMSO served as solvent (negative) controls, potassium dichromate (10 µg/plate), methylmethansulfonate (2 µg/plate) and hycantone (20 µg/plate) served as positive controls.

Two or three replicates per dose level were run and each experiment was repeated three times.

Concentration range used in TA104: 1.9 - 48 µmol/plate; not clear whether this range was applied to TA92, TA98 and TA100, too. A rationale for selection of the tested concentration range is not given.

Remark : According to the illustration available, 2,4-pentanedione was only increasing th e number of spontaneous revertants of TA104 in the dose range of 1.9 - 10 µmol/plate. At concentrations of 10 µmol/plate and above the number of revertants determined was in the control range of 400 – 700 revertants/plate for this particular Salmonella typ himurium strain. Thus the increase of revertants/plate was not in a dose-respons relationship.

The number of spontaneous revertants/plate was in the following limits:

S. typhimurium strain	spontaneous revertants/plate
TA92	40 - 70
TA98	20 - 40

	TA100	100 - 160
	TA104	400 - 700

A substance related mutagenic response was considered significant by the authors after a two-fold (or higher) increase in the number of spontaneous revertants in each of the strains tested.

Result : 2,4-Pentanedione did not show a mutagenic response, i.e. an at least two fold increase in the number of revertants/plate as compared to untreated controls in Salmonella typhimurium strains TA92, TA98 and TA100, respectively.

In TA104 highest number of revertants/plate was about 1,500. 2,4-Pentanedione was classified as "strongly mutagenic" in TA104 within the dose range examined (1.9 - 48 µmol/plate).

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Test substance : commercial product, distilled before use
Reliability : (2) valid with restrictions
Conduction and documentation of study acceptable
Flag : Critical study for SIDS endpoint
13.01.2003 (26)

Type : Ames test
System of testing : Salmonella typhimurium TA98, TA100, TA104 and Escherichia coli WP2uvrA/pKM101
Test concentration : no data
Cycotoxic concentr. : no data
Metabolic activation : with and without
Result : Positive
Method : other: no data
Year : 1989
GLP : no data
Test substance : no data

Remark : The test was conducted according to the preincubation method (20 min at 37°C). No detailed description of test methods and protocol used given by the authors. No information concerning concentration range used.
Result : 2,4-Pentanedione was not mutagenic in Salmonella typhimurium strains TA98 and TA100 and Escherichia coli WP2 uvrA/pKM101 both in the presence and absence of a metabolic activation system.

The compound showed a positive response in the absence of metabolic activation with 2.25 revertants/µg; number of spontaneous revertants/µg not given.
Reliability : (4) not assignable
Conduction and documentation of study very weak. Literature reference available.
Flag : non confidential
16.12.2002 (31)

Type : Sister chromatid exchange assay
System of testing : CHO cells
Test concentration : 0.01 - 1 µmol/ml
Cycotoxic concentr. : 1 µmol/ml
Metabolic activation : without
Result : positive
Method : other
Year : 1989

5. Toxicity **Id** 123-54-6
Date 21.05.2003

GLP : no data
Test substance :

Method : Cultures were incubated for two division cycles (30 h) in the presence of 3 x 10-5 M bromodeoxyuridine. Test compound was added at the same time as bromodeoxyuridine. During the last 4 hours of treatment 0.4 µg/ml of colchicine were added. Finally, metaphase cells were dislodged, centrifuged and suspended in hypotonic buffer, and fixed in ethanol/acetic acid. Fixed cells were heated, stained with Giemsa and scored for SCE. Mitomycin C was used as positive control. Each trial was repeated three times. No metabolic activation system was provided. No information is given on number of metaphases scored, criteria for scoring SCEs, and criteria for cytotoxicity respectively rationale for dose selection.
Result : No detailed description of results; according to the illustration available, significant increase of SCEs per chromosome at the three highest concentrations tested; no information on number of SCEs per cell; toxicity level approximately 1 µmol/ml.
Test substance : no data
Reliability : (4) not assignable
Essential details lacking
Flag : non confidential
13.01.2003 (26)

Type : Bacillus subtilis recombination assay
System of testing : Bacillus subtilis H17 (rec-) and M45 (rec+)
Test concentration : no data
Cycotoxic concentr. : no data
Metabolic activation : with and without
Result : ambiguous
Method : other
Year : 1989
GLP : no data
Test substance :

Method : The liquid Bacillus subtilis/microsome rec-assay was performed. Bacillus subtilis strain H17 (arg-, trp-, recE+) was used as a recombination proficient strain. A derivative of this strain, M45 (arg-, trp-, recE-), was used as the recombination defective strain. Both strains were incubated in liquid suspension and the growth of the bacteria was measured with a turbidity meter. Incubation of both strains with various concentrations of the test compound with and without S9 activation (no further information). Various compounds were run as positive respectively negative controls.
Result : A Compound was evaluated to have a DNA damaging potential if the relative survival (RS) of the rec+-strain was grater than 12.0 % and the S-probit analysis gave a value greater than 0.200. In the tests without metabolic activation RS was 10.21 % and S-probit was 0.050 (negative result), in the tests with S9-mix the values were 12.25 % and 0.076, respectively (ambiguous result).
Test substance : 2,4-pentanedione, purity not indicated
Reliability : (4) not assignable
Essential details lacking, no standard test procedure.
Literature reference available.
Flag : non confidential
16.12.2002 (33)

Type : other
System of testing : Saccharomyces cerevisiae diploid strain D61.M
Test concentration : 0.74, 0.99, 1.48 and 1.96 %
Cycotoxic concentr. : no data

5. Toxicity **Id** 123-54-6
Date 21.05.2003

Metabolic activation	:	without
Result	:	negative
Method	:	other
Year	:	1985
GLP	:	no data
Test substance	:	
Method	:	The diploid strain D61.M was used to study induction of mitotic chromosomal malsegregation, mitotic recombination and point mutation. The treatments were started by pipetting the TS into a growing cell culture at a titer between 3 and 8 x 10E6 cells/ml. Incubation with the TS for 2X4 hours at 28 °C, interrupted by 16 or more hours when cells were placed in an ice-bath. The cells were thereafter plated on selective cycloheximide containing media. Scoring were done after about 6 -7 days for the colony color and colony numbers. The red colonies expressed as frequencies per 10E5 colony-forming units were usually scored. They reflect the cumulative effects of other types of genetic events like point mutation, mitotic recombination or deletion of chromosomal fragments. The presumptive monosomics are found among the white resistant colonies. In the absence of high levels of recombination, chromosomal loss events are confirmed by the concomitant leucine requirements. The white cycloheximide-resistant colonies were examined further both for leucine requirement and to confirm that they were really white. Various compounds were run as positive respectively negative controls.
Result	:	negative
Test substance	:	The test substance was indicated by the authors as acetylacetone (2,5-dipentanone) with a purity of at least 97 %. It is not clear whether 2,4-pentanedione was really tested, because acetylacetone is synonyme to 2,4-pentanedione, but 2,5-dipentanone is not.
Reliability	:	(4) not assignable Essential details lacking. Unclear test substance. No standard test procedure. Literature reference available.
Flag	:	non confidential

16.12.2002 (70)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Cytogenetic assay
Species	:	mouse
Sex	:	male/female
Strain	:	Swiss Webster
Route of admin.	:	inhalation
Exposure period	:	6 hrs/day, 5 consecutive days
Doses	:	0, 100, 400 and 600 ppm
Result	:	negative
Method	:	other: as described in Union Carbide Corporation: Bushy Run Research Center Standard Operating Procedures (SOP)
Year	:	1994
GLP	:	yes
Test substance	:	
Method	:	Male and female Swiss Webster mice (ND4) were exposed to 0 (10 animals per sex), 100 (10 animals per sex), 400 (10 animals per sex) and 600 ppm (14 animals per sex) of 2,4 -pentanedione vapour for five consecutive days, 6 h/day by whole body exposure. Positive control group was treated with cyclophosphamide monohydrate (CP, 30 mg/kg, dissolved in distilled water) by i.p. administration. Bone

marrow from test substance and air-only-treated animals was collected from femurs 6 and 24 hours after final exposure. Bone marrow from positive control animals was collected approximately 24 hours after administration of CP since positive results have been consistently observed at this collection time. Colchicine was dosed by intraperitoneal injection (4 mg/kg) two to three hours prior to sacrifice.

Five hundred cells/animal/sacrifice were scored to determine mitotic index. Hundred metaphase cells/animal/sacrifice were scored for the induction of chromosomal aberrations. Evaluations were made on the chromosome number, specific type of chromosome- or chromatid-type aberrations and exchanges. Gaps were noted but were not included as aberrations when computing the proportion of aberrant cells or for use in statistical analysis. Severely damaged cells (10 or more breakage events) and pulverized cells were scored as 10 aberrations/cell, but no attempt was made to classify the types of damage in such cells.

All animals were observed individually for mortality and overt signs of toxicity twice each day on study days 1-5 and once (in the morning) on study day 6. During exposure, the animals were observed on a group basis. Body weight data were collected for all animals prior to initiation of the first exposure and prior to sacrifice.

Remark : The highest concentration of 600 ppm was approximately 50 % below the LC50 values determined in female rats in studies on the acute toxicity after inhalation.

Chamber concentrations of 2,4-pentanedione were analyzed by gas chromatography twice each hour during the 6-hour exposure periods. The mean detected chamber concentrations of 2,4-pentanedione were 98.7; 415, and 590 ppm for target concentrations of 100, 400, and 600 ppm, respectively. No concentration above the estimated minimum detection limit of 5 ppm was detected in the air-only control chamber atmosphere during the study.

Result : No mortalities, no noteworthy clinical signs and no significant effects on body weight changes were observable in treated animals of the 0, 100 and 400 ppm dose group. Prostration was observed in females of the 600 ppm exposure group. Ten females in the 600 ppm exposure group died between study day 2 and 5.

2,4-Pentanedione did not produce significant, exposure-related increases in the frequencies of chromosomal aberrations (CAs) in the bone marrow of male and female Swiss Webster mice sampled 6 or 24 hours after the final exposure to 0, 100, 400 or 600 ppm. The test substance was therefore not considered to be clastogenic under the conditions of the in vivo assay performed.

Source : Union Carbide Corporation, Danbury CT, USA.
Test substance : purity 99.8 %
Reliability : (1) valid without restriction
Conduction and documentation of study very acceptable. Study report available.
Flag : Critical study for SIDS endpoint
16.12.2002 (67)

Type : Cytogenetic assay
Species : Rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : Inhalation
Exposure period : 6 hrs/day, 5 consecutive days

5. Toxicity **Id** 123-54-6
Date 21.05.2003

Doses	:	0, 100, 400, 600 and 800 ppm
Result	:	Negative
Method	:	other: as described in Union Carbide Corporation: Bushy Run Research Center Standard Operating Procedures (SOP)
Year	:	1990
GLP	:	Yes
Test substance	:	

Method : Ten animals (Sprague-Dawley rats) per sex and dose group were exposed to 0, 100, 400 ppm of 2,4-pentanedione vapour for five consecutive days, 6 h/day. Fourteen animals per sex (7 per harvest time) were exposed to 800 ppm. The doses were chosen based on the results of previous acute and repeated exposure studies. For positive control cyclophosphamide (30 mg/kg) was administered as a single injection to 5 male and 5 female rats. Due to unexpected mortalities among male and female rats exposed to the 800 ppm target concentration, that target concentration was lowered after the second exposure day to 650 ppm for the surviving male rats. An additional target concentration of 600 ppm was added to the study and was administered to both male and female rats by whole body exposure to vapor 6 hours per day for 5 consecutive days. Ten animals per sex (5 at each harvest time) were sacrificed 6 or 24 hours after the fifth exposure, the cyclophosphamide treated (positive control) animals were sacrificed at the same time as the 24 h post-2,4-PD treatment group. Bone marrow cells were harvested and evaluated for chromosomal damage. Colchicine was dosed by intraperitoneal injection (4 mg/kg) two to three hours prior to sacrifice.

Five hundred cells/animal/sacrifice were scored to determine mitotic index. Fifty metaphase cells/animal/sacrifice were scored for the induction of chromosomal aberrations.
Evaluations were made on the chromosome number, specific type of chromosome- or chromatid-type aberrations and exchanges and further classified for deletions and exchanges. Gaps were noted but were not included as aberrations when computing the proportion of aberrant cells or for use in statistical analysis. Severely damaged cells (10 or more breakage events) and pulverized cells were scored as 10 aberrations/cell, but no attempt was made to classify the types of damage in such cells.

Behaviour and appearance of animals were observed prior to, during and following each exposure. Body weights were measured prior to the first and prior to the fifth exposure.

Remark : The highest concentrations of 600 ppm and 650 ppm were approximately 50 % below the LC50 values determined in female rats in studies on the acute toxicity after inhalation.

Less than 50 metaphase spreads per animal were evaluated on 2 of the test animals. One of these animals was a female in the 6 hr sacrifice group exposed to 600 ppm, the second was a female animal in the 24 hr sacrifice group exposed to 400 ppm. The mitotic index in both animals was less than 1 %.

Chamber concentrations of 2,4-pentanedione were analyzed by gas chromatography approximately 6 times during each 6-hour exposure period. The mean detected chamber concentrations of 2,4-pentanedione were 100.6; 414; 609 and 695 ppm for target concentrations of 100, 400, 600 and 800 ppm, respectively. The 800 ppm target concentration was lowered to 650 ppm after the second day of exposure due to animal deaths. No TS was found in the air-only (negative) control chamber.

Result : All female rats and two out of fourteen male rats exposed to 800 ppm died

or were sacrificed moribund between study day 1 and 3. Among the 14 male und 14 female rats exposed to 600 ppm, three female rats died during the exposure regime. Clinical signs prior to death were ataxia and/or prostration. Male rats exposed to 800 ppm and both male and female rats exposed to 600 ppm lost weight. In the 400 ppm exposure group both male and female rats had depressed body weight gains during the exposure regime.

2,4-Pentanedione produced one statistically significant increase in the incidence of chromosomal aberrations in the 6 h sacrifice group of male rats exposed at a target concentration of 100 ppm as compared to air-exposed (negative control). There were no statistically significant increases in the incidence of chromosomal aberrations among male rats exposed at target concentrations of 400, 600 or 800 ppm in the 6 h sacrifice group. No statistically significant or concentration-related increases in the incidence of chromosomal aberrations were observed among 2,4-pentanedione-exposed male rats in the 24 h sacrifice group or among any of the 2,4-pentanedione-exposed female rats. Because the statistically significant observation among male rats exposed at 100 ppm was small in magnitude (5.2 %) and did not persist at the 24 h sacrifice, 2,4-pentanedione was not considered to have biologically significant clastogenic activity in rats under the conditions of this test by the authors of the report.

Source : Union Carbide Corporation, Danbury CT, USA.
Test substance : purity > 99 %
Reliability : (1) valid without restriction
Conduction and documentation of study acceptable. Study report available.
Flag : Critical study for SIDS endpoint
16.12.2002 (60)

Type : Dominant lethal assay
Species : rat
Sex : male
Strain : Fischer 344
Route of admin. : inhalation
Exposure period : 6 h/day for 5 consecutive days
Doses : 0, 100, 400 and 700 ppm
Result : ambiguous
Method : EPA OPPTS 870.5450
Year : 1987
GLP : yes
Test substance :

Method : Male Fischer F-344 rats (COBS CDF F344/CrlBR), 20 per group, were exposed to 2,4-pentanedione vapour at target exposure concentrations of 0, 100, 400 and 700 ppm (mean analytical values of 0, 99.1, 412 and 694 ppm, respectively) for five consecutive days, six hours per day to determine the dominant lethal potential of 2,4-pentanedione. Male rats were subsequently (beginning the day after the last exposure) bred to naive (unexposed) females of the same strain in a 2:1 manner, for eight consecutive weeks. Each female was removed when evidence of copulation (copulation plug or vaginal smear) was observed or weekly, whichever came first, and replaced weekly by additional naive females, two females: each male (2:1 manner), for a total of eight consecutive weeks. The males were observed daily for clinical signs of toxicity, weighed weekly and necropsied after the eighth week of mating. At necropsy, brain, testes (weighed together) and thymus weights were taken and these tissues were fixed for possible subsequent histopathology. These tissues from high dose and control males were examined histologically. All females were observed daily during the mating for evidence of copulation and daily from

gestational day 0 (date of plug or sperm) to sacrifice for clinical signs of toxicity. They were sacrificed on gd 15 and ovarian corpora lutea, and uterine implantation sites: nonlive (early and late resorptions) and live were counted and recorded.

Remark : By the study authors it was concluded that at 400 and 700 ppm possible indications of reproductive and gestational effects and a weak transient dominant lethal effect during weeks 2-4 at 400 and 700 ppm were seen. However, on closer examination of the data it turned out that the difference of corpora lutea for week two between the negative control group (unexposed animals) and the 700 ppm-group is 10.6 to 9.7 which is a difference of 0.9. As the standard deviation in the negative control group is 1.2 and in the 700 ppm-group is 1.9 there is no real basis for the interpretation that the lower value in the 700 ppm-group might indicate a reduction of the number of corpora lutea per dam. In addition, statistical significance of the slightly lower value in the 700 ppm-group could not be established. Therefore, this difference has to be evaluated as a random effect.
The increased postimplantation loss in per cent assumed as possible mutagenic effect at 400 and 700 ppm is based on the following data: 0 ppm=2.3; 400 ppm=11.8 and 700 ppm=8.7. However, upon close examination of the complete data for week two, namely also of the standard deviations (s.d.) it is obvious that the value of 11.8 (400 ppm) has a s.d. of 31.3 and that of 8.7 (700 ppm) one of 25.3. Therefore, because of this data situation, it is not justified to speak of a "slight increase" of postimplantation loss. These data might at best be interpreted as inconclusive and on no account towards the assumption of a mutation potential of the test material. A similar situation exists for the data obtained in week 4 after the exposure. In the report an indication for a slightly reduced number of total and viable implants per litter is postulated at 700 ppm. The data for total implants/litter are 9.7 in the negative control group and 8.4 in the 700 ppm group. If one takes into consideration the s.d. which are 2.9 and 3.3, respectively, then there seems to be no basis for the interpretation for a "slight reduction". In addition, again there was no justification by statistical significance. Therefore, these two different values cannot be taken as sign for a possible potential of the test material to induce mutations in the Dominant Lethal Test system. The same holds true for the statement that viable implants per litter were reduced. Also, for week four a preimplantation loss is discussed as being increased in the 700 ppm group. In this case the statistical evaluation resulted in a weak significance. However, the data of the 700 ppm group in comparison to those of the negative control group are not really convincing with regard to the variability expressed by the s.d. values: 16.1 with 21.2 s.d. (negative control); 29.2 with 25.0 s.d. (700 ppm). Although there was weak statistical significance of the 700 ppm value, the very high s.d. in both cases indicates high variability of the data from individual animals. Therefore, this significance is a single calculatory value in the whole study without convincing values in all other treatment groups which would point to a tendency of the test material to possibly induce lethal mutations. Without further data this is not enough basis for assuming a mutational potential of the test material.
All other data from week 1,3,5-8 do not indicate any tendency for induction of dominant lethal effects.

Result : Males exposed to 400 and 700 ppm exhibited reduced body weights at week 1 (after the five days exposure period). At week 2, only the males at 700 ppm still exhibited a reduced body weight. Weight loss was exhibited in all groups for the exposure period (due to the stress of inhalation exposure), but the amount lost exhibited a clear exposure-related pattern. For weeks 1-2, and 1-9, males at 700 ppm gained significantly more weight than did controls. There were no other differences among groups for male

body weight or weight gain. Treatment related clinical signs of toxicity were restricted to males exposed to 700 ppm and included aggression, red occular discharge and red perioral encrustation. There were no effects of treatment on clinical or gross observations at the time of necropsy of the males, nor were there any effects on terminal body weight or organ weights, expressed as absolute weights or relative to body or brain weight. Histological examination of male brain, thymus and testes indicated no treatment-related microscopic lesions. Reproductive parameters for the males and females were affected only on week 3. For week 3, the number of pregnant females was slightly reduced at 400 and 700 ppm so that the female fertility index was also lower. Gestational parameters exhibited apparent treatment-related effects on weeks 2 and 4 of mating. For week 2 the number of corpora lutea per dam were reduced and for both weeks 2 and 4, the number of total and viable implants per dam were reduced at 700 ppm, but not statistically significant. Postimplantation loss was slightly (but also not statistically significantly) increased at 400 and 700 ppm at week 2 and preimplantation loss was significantly increased at week 4. The dominant lethal factor, was increased slightly at 700 ppm for weeks 2 and 4. When the data for all eight weeks of mating were pooled, there were no effects of treatment on reproductive or gestational parameters.
Conclusion by the authors:
Exposure of male F-344 rats for five days to 2,4-pentanedione vapour and subsequent mating to naïve (unexposed) females of the same strain for eight weeks produced male toxicity at 400 and 700 ppm and possible indications of reproductive and gestational effects and a weak transient dominant lethal effect during weeks 2-4 at 400 and 700 ppm. This time period corresponds to sperm exposed during the spermatid stage of spermatogenesis. Pooled reproductive and gestational data from all eight mating weeks indicated no effects. The NOEL was 100 ppm.

Source : Union Carbide Corporation, Danbury CT, USA.
Test substance : purity 99.2 %
Reliability : (2) valid with restrictions
Conduction and documentation of study acceptable. Literature reference and study report available.
Flag : Critical study for SIDS endpoint
16.12.2002 (50) (59)

Type : Micronucleus assay
Species : Mouse
Sex : male/female
Strain : Swiss Webster
Route of admin. : i.p.
Exposure period : 30, 48 and 72 hours
Doses : 0, 200, 400 and 650 mg/kg b.w.
Result : Positive
Method : other
Year : 1986
GLP : Yes
Test substance :

Method : 5 Male and 5 female Swiss Webster mice per dose group and time point received single i.p. injections of 0, 200, 400 and 650 mg 2,4-pentanedione/kg bw. Test doses were based on the results of range finding studies after i.p. administration of 2,4-pentanedione and correspond to 25 % (200 mg/kg), 50 % (400 mg/kg) and 80 % (650 mg/kg) of the LD50 after i.p. injection, respectively. Vehicle (water) and positive controls (triethylenemelamine, 0.5 mg/kg) were included. For the evaluation of micronucleated PCEs peripheral blood samples from 2,4-pentanedione-treated animals were collected after 30, 48 and 72 hours, respectively.

Blood from positive control animals was collected after 30 hours only. The polychromatic:normochromatic erythrocyte ratio for approximately 1000 total cells was calculated as an estimate of the cytotoxicity of the test agent. A minimum of 1000 polychromatic erythocytes was examined microscopically for each animal per sample time, unless cytotoxicity of the test material prevented this goal.

Result : There was no evidence of significant or dose-related decreases in the PCE:NCE ratio for either sex at any of the sample times. The only significant decrease in the PCE:NCE ratio (56.5 % of the control) was observed for the positive control animals.
Statistically significant increases in the incidences of micronucleated PCEs was observable at the 30 and 48 hours blood collection time points in a dose dependent manner for both male and female mice treated with 400 mg/kg or 650 mg/kg. A maximum incidence of 0.69 % (3.8 times the vehicle controls) PCEs with micronuclei was observed for the highest dose tested (650 mg/kg).
After 72 hours the number of PCEs with micronuclei returned to control values. The 0.5 mg/kg dose of triethylenemelamine used as positive control produced significant increase in numbers of micronuclei in the PCEs of both male and female mice (at least a 6-fold in magnitude).
Based on the results obtained 2,4-pentanedione is considered to induce micronuclei under the conditions of the test system in male and female Swiss Webster mice.

Source : Union Carbide Corporation, Danbury CT, USA.
Test substance : purity 99,2 %
Reliability : (2) valid with restrictions
Conduction and documentation of study very acceptable. Study report available.
Flag : Critical study for SIDS endpoint
16.12.2002 (65)

Type : Micronucleus assay
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : i.p.
Exposure period : 6, 24 and 48 hours
Doses : 50, 100, 200, 400 and 650 mg/kg b.w.
Result : negative
Method : other
Year : 1994
GLP : yes
Test substance : other TS

Method : Animals were housed 2/cage and had access to food and water ad libitum except during the treatment period. Injection volumes for all animals were based on individual body weights determined on the day of treatment. The animals were sacrificed by carbon dioxide aspyhxiation. Bone marrow was sampled from 2,4-pentanedione-treated and vehicle control rats at 6, 24, and 48 hours and from positive control rats at 24 hours after treatment. Femurs were removed and the bone marrow was aspirated with a syringe into fetal bovine serum. Nucleated cells were then removed from the bone marrow preparations using a cellulose column. Bone marrow cells were pelleted by centrifugation of the column eluate. The cell was smeared on a microscope slide. Slides were stained with Giemsa.

Remark : Due to unexpected deaths at the 400 and 650 mg/kg doses, two additional dose levels (50 and 100 mg/kg b.w.) were added to the study.

The doses of 400 and 650 mg/kg b.w. corresponded to 52 and 86 %,

5. Toxicity **Id** 123-54-6
Date 21.05.2003

respectively, of the acute oral toxicity LD50-values determined in rats.

Result : All males and females in the 650 mg/kg b.w. group and 4 males in the 400 mg/kg group died prior to their scheduled six hour sacrifice. Findings in the 400 and 650 mg/kg groups included hypoactivity, incoordination, prostration, whole body tremor, tonic convulsions, excessive vocalization, urogenital area wetness, labored respiration, gasping, perinasal and perioral wetness, nasal discharge, periocular encrustation and lacrimation. Signs of toxicity were also observable in the 200 mg/kg group. No signs of toxicity were observed in animals of either sex in the 50 or 100 mg/kg groups at any time.

No significant changes in the proportion of polychromatic erythrocytes (PCE) were observed in the 2,4-pentanedione-treated rats of either sex at any sampling time. The mean percentage of micronucleated PCE were 0.30, 0.19 and 0.29 for the vehicle control males and 0.12, 0.12 and 0.31 for the vehicle control females at 6, 24, and 48 hours, respectively. Among 2,4-pentanedione-treated male rats, the mean percentage of micronucleated PCE ranged from a low of 0.11 at 100 mg/kg at the 24 hour sampling time to a high of 0.31 at 50 mg/kg at the 6 hour sampling time. Among 2,4-pentanedione-trated female rats, the mean percentage of micronucleated PCE ranged from a low of 0.11 at 100 mg/kg at the 6 hour sampling time to a high of 0.39 at 200 mg/kg at the 24 hour sampling time. A statistically significant increase in the frequency of micronucleated PCE was observed only at the 24 hour sampling time in female rats in the 200 mg/kg treatment group. However, no significant increase in the frequencies of micronucleated PCE were observed at the 24 hour sampling time in females treated with 50 or 100 mg/kg or in rats of either sex at any other 2,4-pentanedione treatment dose or sampling time. Due to the conservative nature of the statistical analysis performed, the small magnitude of the increase in micronuclei frequency, the lack of dose response, and the sex-specific nature of the response, the statistically significant increase observed in the 200 mg/kg females was not considered to be treatment related or biologically significant. The mean percentages of micronucleated PCE in the cyclophosphamide treated positive control group were 0.95 % and 2.08 %, for males and females, respectively. Numbers of micronuclei in the vehicle control animals were in an acceptable range for this test system.

In conclusion 2,4-pentanedione did not produce significant, treatment related increases in the incidence of micronucleated polychromatic erythrocytes in male and female Sprague-Dawley rats assessed at 6, 24 and 48 hours following a single administration by i.p. injection. Therefore, 2,4-pentanedione was not considered to an inducer of micronuclei in male and female rats under the conditions of this in vivo assay.

Source : Union Carbide Corporation, Danbury CT, USA.
Reliability : (1) valid without restriction
Conduction and documentation of study very acceptable. Study report available.
Flag : Critical study for SIDS endpoint
16.12.2002 (62)

Type : Micronucleus assay
Species : Mouse
Sex : male/female
Strain : Swiss Webster
Route of admin. : Inhalation
Exposure period : 6 hrs/day for 5 consecutive days
Doses : 0, 100, 400 and 600 ppm
Result : Negative

5. Toxicity **Id** 123-54-6
Date 21.05.2003

Method	:	EPA OTS 798.5395
Year	:	1993
GLP	:	Yes
Test substance	:	
Method	:	5 Male and 5 female Swiss Webster mice per dose group were exposed to 2,4-pentanedione-vapour at concentrations of 0,100, 400 and 600 ppm by whole body exposure. The highest concentrations chosen was about 50 % below the LC50 values determined in acute inhalation toxicity studies with female rats. Bone marrows from 2,4-pentanedione-treated as well as air-only-control and positive control (triethylenemelamine, 30 mg/kg i.p.) animals were collected from femurs 24 hours after final exposure and examined for the formation of micronucleated polychromatic erythrocytes. The PCE.NCE ratio for a total of 1000 cells for each animal was calculated to provide an estimate of cytotoxicity. A minimum of 1000 PCE for each animal was scored for the presence of micronuclei unless the cytotoxicity of the test substance prevented this. All animals were observed individually for mortality and signs of toxicity. During exposure, observations were recorded on a group basis. Body weight data were collected for all animals prior to the first exposure and immediately after the last exposure.
Remark	:	Chamber concentrations were analyzed approximately once each hour during the 6 h exposure by gas chromatography. The mean analysed chamber concentrations of 2,4-pentanedione were 97, 405, and 592 ppm for target concentrations of 100, 400, and 600 ppm, respectively.
Result	:	No noteworthy clinical signs in any of the 2,4-pentanedione treated male or female mice were observed at 0, 100 and 400 ppm. Three female mice in the 600 ppm exposure group died during the study. Substance related effects were evident as hypoactivity, prostration, urogenital wetness, gasping, slow respiration and blepharospasm in on or more of these females. No significant effects on weight changes were noted. There were no significant differences in the PCE to NCE ratios between 2,4-pentanedione-exposed and control animals. The number of micronucleated PCE/1000 PCE was between 0 and 6/animal in both the vehicle control and the 2,4-pentanedione-exposed mice. The mean percentage of micronucleated PCE was 0.34 for the air-only-exposed males and 0.14 for the air-only-exposed females. Among TS-exposed males, the mean percentage of miconucleated PCE ranged from a low of 0.20 at 400 and 600 ppm to a high of 0.28 at 100 ppm. Among TS-exposed females, the mean percentage of micronucleated PCE ranged from a low of 0.10 at 100 ppm to a high of 0.22 at 400 ppm. Trietylenemelamine, used as a positive control substance for this study, produced highly significant increase in numbers of micronuclei in both sexes. Numbers of micronuclei in the vehicle control animals were in a low and acceptable range for this test system. In conclusions 2,4-pentanedione did not produce significant or dose-related increases in the frequency of micronucleated polychromatic erythrocytes in the bone marrow of Swiss-Webster mice assessed at 24 hrs after whole body exposure to 2,4-pentanedione vapor 6 hours each day for 5 consecutive days. Therefore, the TS was not considered to be an inducer of micronuclie under the conditions of this in vivo assay.
Source	:	Union Carbide Corporation, Danbury CT, USA.
Test substance	:	purity 99,92 %
Reliability	:	(1) valid without restriction Conduction and documentation of study very acceptable. Study report available.
Flag	:	Critical study for SIDS endpoint

5. Toxicity **Id** 123-54-6
Date 21.05.2003

16.12.2002 (61)

Type	:	Micronucleus assay
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation
Exposure period	:	6 hrs/day for 5 consecutive days
Doses	:	0, 100, 400 and 600 ppm
Result	:	negative
Method	:	EPA OTS 798.5395
Year	:	1993
GLP	:	yes
Test substance	:	

Method : 5 Male and 5 female Sprague-Dawley rats per dose group were exposed to 2,4-pentanedione-vapour at concentrations of 0, 100, 400 and 600 ppm by whole body exposure. The highest concentrations chosen was about 50 % below the LC50 values determined in acute inhalation toxicity studies with female rats. Bone marrows from 2,4-pentanedione-treated as well as air-only-control and positive control (triethylenemelamine, 30 mg/kg i.p.) animals were collected from femurs 24 hours after final exposure and examined for the formation of micronucleated polychromatic erythrocytes. The PCE.NCE ratio for a total of 1000 cells for each animal was calculated to provide an estimate of cytotoxicity. Aminimum of 1000 PCE for each animal was scored for the presence of micronuclei unless the cytotoxicity of the test substance prevented this. All animals were observed individually for mortality and signs of toxicity. During exposure, observations were recorded on a group basis. Body weight data were collected for all animals prior to the first exposure and immediately after the last exposure.

Remark : Chamber concentrations were analyzed approximately once each hour during the 6 h exposure by gas chromatography. The mean analysed chamber concentrations of 2,4-pentanedione were 97, 405, and 592 ppm for target concentrations of 100, 400, and 600 ppm, respectively.

Result : There were no noteworthy clinical signs of toxicity in male or in female rats exposed to 100 or 400 ppm. Three male rats in the 600 ppm exposure group had perinasal encrustation an day 1, but no other clinical signs during the study. Three of the 5 female rats in the 600 ppm exposure group died on days 2-4. Prostration and slow respiration were observed in one female rat prior to death. Male rats exposed at 400 ppm had significantly lower body weight gains and male rats exposed at 600 ppm had significant body weight losses. Female rats had significant body weight losses after exposure at 400 or 600 ppm.

There were no significant differences in the PCE to NCE ratios between 2,4-pentanedione and control animals. The number of micronucleated PCE/1000 PCE was between 0 and 7/animal in both the vehicle control and the 2,4-pentanedione-exposed rats. The mean percentage of micronucleated PCE was 0.30 for the air-only-exposed males and 0.34 for the air-only-exposed females. Among TS-exposed males, the mean percentage of miconucleated PCE ranged from a low of 0.24 at 400 ppm to a high of 0.46 at 600 ppm. Among TS-exposed females, the mean percentage of micronucleated PCE ranged from a low of 0.10 at 400 ppm to a high of 0.24 at 100 ppm.

Trietylenemelamine, used as a positive control substance for this study, produced highly significant increase in numbers of micronuclei in both sexes. Numbers of micronuclei in the vehicle control animals were in a low and acceptable range for this test system.

In conclusions 2,4-pentanedione did not produce significant or dose-related increases in the frequency of micronucleated polychromatic erythrocytes in the bone marrow of Sprague-Dawley rats assessed at 24 hrs after whole body exposure to 2,4-pentanedione vapor 6 hours each day for 5 consecutive days. Therefore, the TS was not considered to be an inducer of micronuclie under the conditions of this in vivo assay.

Source : Union Carbide Corporation, Danbury CT, USA.
Test substance : purity 99,92 %
Reliability : (1) valid without restriction
Conduction and documentation of study very acceptable. Study report available.
Flag : Critical study for SIDS endpoint
16.12.2002 (61)

Type : other: mouse spermatogonia chromosomal aberration test
Species : mouse
Sex : male
Strain : NMRI
Route of admin. : drinking water
Exposure period : 24 and 48 hours
Doses : 800 mg/kg b.w.
Result : negative
Method : OECD Guide-line 483 "Genetic Toxicology: Mammalian Germ-cell Cytogenetic Assay"
Year : 2000
GLP : yes
Test substance :

Method : 6 Animals each were used for both vehicle and positive controls as well as test substance treated groups. 2,4-pentanedione was administered in deionised water to male NMRI mice at a dose of 800 mg/kg b.w. which was close to the MTD as shown in a preceding range-finding test. For the investigation of chromosomal aberrations in germ cells spermatogonial cells were prepared 24 and 48 hours after single test substance administration. 5 male mice were examined at each time point. At least 100 metaphases per animal were scored for cytogenetic damage. Gaps, breaks, fragments, deletions, exc hanges and chromosomal disintegrations were recorded as structural chromosome aberrations. A negative vehicle control (deionised water, 10 ml/kg bw) and a well proven positive control (Adriblastin, 5 mg/kg bw) were included in this assay. Statistical analysis of results observed was included and confirmed by the non-parametric Mann. whitney test.
Remark : In a preceding study the bioavailability of the test material was confirmed. It was determined that 800 mg/kg bw administered orally were close to the MTD as shown by signs of toxicity in the treated animals such as reduction of spontaneous activity, eyelid closure, apathy and tremor. In this previous test the systemic distribution of the test substance was also checked and it was found that after oral adm inistration the test substance was detectable in blood serum up to four hours post-treatment.
Result : After preparation and examination of spread spermatogonial cells (100 cells of each animal, i.e. 500 per dose and time point were analysed) no reduction in the mitotic index could be observed, indicating that 2,4-pentanedione at the indicated dose and the indicated application route was not cytotoxic for spermatogonial cells. No statistically significant or biologically relevant increase in the number of numerical and structural aberration as compared to vehicle treated controls could be found. Aberration rates were 0.8 % and 1.0 % for the 24 h and the 48 h treatment, respectively, as compared to the vehicle control value of 0.6 %. The mean

aberration frequencies observed after treatment with 2,4-pentanedione were consistently below 2 % aberrant cells exclusive gaps, given as the upper limit of a tolerable vehicle control value. The positive control showed a statistically significant response (9 % aberration rate excluding gaps). In conclusion, 2,4-pentanedione is being considered non-mutagenic under the conditions of this assay.

Source : WACKER CHEMIE GmbH, Burghausen, Germany.
Test substance : purity: 99,59 %
Reliability : (1) valid without restriction
Conduction and documentation of study according to OECD guidelines. Study report available.
Flag : Critical study for SIDS endpoint
16.12.2002 (43)

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : Rat
Sex : Female
Strain : Fischer 344
Route of admin. : Inhalation
Exposure period : gestational days (GD) 6-15
Frequency of treatm. : 6 h/day
Duration of test : until GD 21
Doses : 0, 50, 200, 400 ppm
Control group : yes, concurrent vehide
NOAEL maternal tox. : = 200 ppm
NOAEL teratogen. : = 400 ppm
NOAEL Fetotoxicity : = 50 ppm
LOAEL Fetotoxicity : = 200 ppm
LOAEL Maternal Toxicity : = 400 ppm
Method : other
Year : 1986
GLP : yes
Test substance :

Method : Timed-pregnant Fischer F-344 rats (Harlan Fischer F-344/HarBR) were exposed to 2,4-pentanedione vapour by inhalation on gestational days (gd) 6 to 15 at exposure target concentrations of 0, 50, 200 and 400 ppm (0, 52.7, 202 and 398 ppm mean analytical concentrations, respectively) to evaluate the embryotoxic and fetotoxic (including teratogenic) potential of the TS administered during organogenesis. The day a copulation plug was found was designated gestational day (gd) 0. Twenty-five plug-positive females were assigned to each experimental group. Clinical observations were recorded daily, and maternal body weights were taken on gd 0, 6, 9, 12, 15 and 18. At scheduled necropsy on gd 21 (CO_2 asphyxiation), dams were evaluated for body weight, liver and thymus weights, gravid uterine weight, and status of implantation sites (i.e. resorptions, dead fetuses, live fetuses). Maternal brains were removed, fixed and examined histopathologically. Live fetuses were dissected from the uterus, counted,

weighed and sexed and examined for external abnormalities. Approximately one-half of the live fetuses in each litter was examined for visceral abnormalities. These fetuses were then decapitated and their heads fixed in Bouins solution and examined for soft tissue craniofacial malformations. The remaining intact fetuses in each litter were eviscerated, fixed in alcohol, stained with alizarin red S, and examined for skeletal defects and deficits.

Remark : No decompositional changes or chamber loss of metered 2,4-pentanedione. The mean detected camber concentrations of 2,4-pentanedione were 52.7, 202 and 398 ppm for target concentrations of 50, 200 and 400 ppm, respectively.

Result : Maternal toxicity: significantly reduced body weight gain at 400 ppm; liver weight significantly increased at 200 ppm; no further significant effects determined; Fetal toxicity: significant reduction in female body weight per litter at 400 ppm (all fetuses, males and females approximately 10 %) and at 200 ppm (all fetuses, and males but not females approximately 3 %); one visceral variation (partial fetal atelectasis) significantly increased at 400 ppm; 17 out of 79 observed skeletal variation exhibited significant changes in incidence and indicated a consistent pattern of reduced ossification in the 400 ppm group (for example poorly or unossified phalanges, unossified cervical or poorly ossified thoracic centrum); no differences among the groups in the incidence of external, visceral or skeletal malformations; no further treatment related effects.

There was no maternal mortality in this study. Maternal toxicity was indicated by reduced body weights on gd 9, 12, 15, and 18 but not on gd 21, and reduced weight gain for the intervals gd 6-9, 6-12, 6-15 (exposure period) and gd 6-18, but not for the post-exposure period (gd 15-21). There were no treatment-related effects on maternal liver, thymus or gravid uterine weight, or on body weight (absolute or corrected for gravid uterus) at sacrifice; histologic examination of the maternal brains showed no pathological effects related to treatment. There were also no effects of treatment on the number of ovarian corpora lutea, of total, non-viable or viable implantations per litter, or on pre- or post-implantation loss or on sex ratio. There were no maternal deaths, early deliveries or abortions. Pregnancy rate was high and equivalent across all treatment groups. One dam each at 0, 50 and 200 ppm carried a totally resorbed litter on gd 21. Two dams at 400 ppm had totally resorbed litters on gd 21. Clinical observations were made daily throughout the study. Most of the observations were limited to the eyes, nose and blood at the vaginal orifice and only in a few dams per group. In addition, urogenital area wetness was present in a few dams only at 0, 50, 200 ppm (not at 400 ppm). At sacrifice on gd 21, there was no effect of exposure on maternal body weight, maternal body weight corrected for gravid uterine weight or on absolute or relative (to corrected body weight) thymus weight. Absolute and relative liver weight was elevated at 200 but not at 400 ppm. Administration of TS vapour by inhalation to timed-pregnant Fischer F-344 rats during organogenesis at 0, 50, 200 and 400 ppm resulted in maternal toxicity at 400 ppm. Fetotoxicity was observed at 200 and 400 ppm in terms of reduced fetal weights per litter (approximately 3 and 10 %, respectively) and at 400 ppm in terms of a consistent pattern of reduced fetal ossification. There was no evidence of embryotoxicity or teratogenicity at any exposure concentrations employed, including those which produced maternal toxicity.

Based on a significantly reduced body weight gain in the 400 ppm exposure group the NOAEL/LOAEL derived for maternal toxicity is 200 and 400 ppm, respectively.

The NOAEL/LOAEL for developmental toxicity is 50 and 200 ppm, respectively, which is based on reduced fetal weights in male fetuses at 200 ppm and in male and female fetuses at 400 ppm and a consistent pattern of reduced fetal ossification at 400 ppm.

The NOAEL for embryotoxicity and teratogenicity is 400 ppm (highest dose tested).

Source : Union Carbide Corporation, Danbury CT, USA.
Test substance : purity 99.5 % at pre study analysis and 99.3 % at post study analysis
Reliability : (1) valid without restriction
Conduction and documentation of study very acceptable.
Literature reference and study report available.
Flag : Critical study for SIDS endpoint
16.12.2002 (49) (55)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Remark : Irritant Properties on Humans
Result : 2,4-Pentanedione was reported to be mildly irritating to skin and mucous membranes.
Reliability : (2) valid with restrictions
Information retrieved from secondary literature without access to original literature reference.
Flag : Critical study for SIDS endpoint
16.12.2002 (2)

Remark : Acute Local and Acute Systemic Effects
Result : Acute local effects: 2,4-Pentanedione causes irritant effects which have been reported to be slight. Changes are readily reversible and disappear after end of exposure.

Acute systemic effects: After inhalation 2,4-pentanedione causes moderate effects and may involve both reversible and irreversible changes which are not strong enough to cause death or permanent injury.
Reliability : (2) valid with restrictions
Information retrieved from secondary literature without access to original literature reference.
Flag : Critical study for SIDS endpoint
16.12.2002 (2)

Remark : General Effects to Humans
Result : It has been reported that 2,4-pentanedione is appreciably more toxic by oral ingestion and vapor inhalation than either 1,2- or 1,4-diketones and saturated monoketones. The acute oral toxicity is high and internal consumption should be avoided. It is comparable in this respect to mesityl oxide. Breathing 2,4-pentanedione vapors may cause dizziness, headache, nausea, vomiting, and loss of consciousness. Skin irritation appears less

hazardous. However, eye burns may result from a large application, similar to soap.

Reliability : (2) valid with restrictions
Information retrieved from secondary literature without access to original literature reference.

Flag : Critical study for SIDS endpoint

16.12.2002 (2)

5.11 ADDITIONAL REMARKS

Type : Neurotoxicity

Remark : According to the illustrations available, a dose of 200 mg 2,4-pentanedione/kg bw/day given on 107 consecutive days to rats, produced no changes of sensory conduction velocities, motor conduction velocities and residual latency.

Test substance : 2,4-pentanedione, purity not indicated

Reliability : (4) not assignable
Essential details lacking. Literature reference available.

Flag : non confidential

13.11.2002 (37)

Type : Neurotoxicity

Remark : Neurotoxic evidence was revealed by 2,4-pentanedione. Significant slowing of motor conduction velocities (MCV) began to be observed in the 2,4-pentanedione group at 10^{th} week. At 8th week, a significant decrease in sensory conduction velocities (SCV) was also observed. In the 2,4-pentanedione group SCV values were slowed more than the MCV values. In the 2,4-pentanedione group, a significant decrease in nerve action potentials (NAP) amplitudes was observed at 16th week and that in muscle action potentials (MAP) amplitudes at 28th week. Residual latencies (RL) and motor distal latencies (DL) were not affected.

Test substance : 2,4-pentanedione, purity not indicated

Reliability : (4) not assignable
Essential details lacking. Literature reference available.

Flag : non confidential

16.12.2002 (41)

Type : Neurotoxicity

Method : Cortical neuronal cells from embryonal rats were incubated with 2,4-pentanedione and general cytotoxicity as well as the intracellular content of glial fibrillary acid protein (GFAP), neuron-specific enolase (NSE), and neurofilaments were measured three and seven days after first dosing. The cultures consisted of 85-90 % neurons and 10-15 % glia cells and were incubated with 1, 5, 10, 50 and 100 µg/ml. N-Heptane and DMSO were used as controls.

Result : 2,4-Pentanedione showed neither acute nor delayed cytotoxic potential even in high concentrations, whereas the nonneurotoxic solvent n-heptane was acutely cytotoxic. On day seven, but not an day three, neurofilaments were affected with a NOEC of 1 µg/ml and EC50 of 80 µg/ml. Neurofilaments are essential constituents of the neuronal axon and regulate axonal transport. The GFAP-NSE ratio in the brain as a sensitive indicator for a selective neuronal degeneration was only slightly influenced by 2,4-pentanedione; the content of glial fibrillary acid protein was not decreased and the neuron-specific enolase was only affected an day three

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with an NOEC of 50 µg/ml.

Test substance : 2,4-pentanedione, purity less than 99 %
Reliability : (4) not assignable
No standard test procedure. Literature reference available.
Flag : non confidential
16.12.2002 (45)

6. Analyt. Meth for Detection and Identification **Id** 123-54-6
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6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7. Eff. Against Target Org. and Intended Uses **Id** 123-54-6
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7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8. Meas. Nec. to Prot. Man, Animals, Environment **Id** 123-54-6
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8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

9. References **Id** 123-54-6
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(1) ACETYLACETONE: HAZARDOUS SUBSTANCES DATA BANK (HSDB) search, 1997.

(2) ACETYLACETONE: HAZARDOUS SUBSTANCES DATA BANK (HSDB) search, 2000.

(3) Arnett, E.M. and Harrelson, J.A., Gazz. Chim. Ital. 117, 23 7-243 (1987)

(4) Auer-Technikum, ed. 12, Auergesellschaft mbH, Berlin, 500-505 (1989)

(5) Ballantyne, B. (2001) Systemic toxicity from repeated cutaneous contact with 2,4-pentanedione. Vet. Human Toxicol. 43, 14 - 18

(6) Ballantyne, B., Dodd, D.E., Myers, Nachreiner, D.J. (1986) The acute toxicity and primary irritancy of 2,4-pentanedione. Drug and Chemical Toxicology, 9, 133-146

(7) Berezina, Z.B. (1987) On the toxicity of acetylacetone. GISAAA, Gigiena i Sanitaiya, 52 (10), 88

(8) Bringmann, G. and Kuehn, R. (1982) Ergebnisse der Schadwirkung wassergefährdender Stoffe gegen Daphnia magna in einem weiterentwickelten standardisierten Testverfahren. Z. Wasser Abwasser Forsch. 15, 1-6.

(9) Bringmann, G. and Kuehn, R., Mitt. Int. Theor. Angew. Limnol. 21, 275-284 (1978)

(10) Bringmann, G. and Kuehn, R., Vom Wasser 50, 45-60 (1978)

(11) Bringmann, G. and Kuehn, R., Z. Wasser Abwasser Forsch. 10, 161-166 (1977)

(12) Bringmann, G. and Kuehn, R., Z. Wasser Abwasser Forsch. 10, 87-98 (1977)

(13) Bringmann, G. and Kuehn, R. Comparison of the Toxicity Thresholds of Water Pollutants to Bacteria, Algae, and Protozoa in the Cell Multiplication Inhibition Test. Water Res. 14, 231-241, 1980.

(14) Brooke, L.T. et al., acute toxicity of organic chemicals to Fathead minnows, Center of Lake Superior Environmental Studies , University of Wisconsin-Superior, Vol. I (1984)

(15) Brooke, L.T. et al., acute toxicity of organic chemicals to Fathead minnows, Center of Lake Superior Environmental Studies, University of Wisconsin-Superior, Vol. II (1984)

(16) Buxton, G.V., Greenstock, C.L., Helman, W.P., and Ross, A.B. (1988) Critical Review of Rate Constants for Reactions of Hydrated Electrons, Hydrogen Atoms and Hydroxyl Radicals (OH/O-) in Aqueous Solution. J. Phys. Chem. Ref. Data 17 (2), 513ff.

(17) Carlson, R.W., Comp. Biochem. Physiol. 95C, 181-196 (1990)

(18) Carpenter, C.P., Smyth, H.F., Pozzani, U.C. (1949) The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. J. Ind. Hyg. Toxicol. 31, 343-346

(19) CRC Handbook of Chemistry and Physics,(1996), 77th ed., CRC Press, Boca Raton, Florida

(20) Dodd, D.E., Garman, R.H., Pritts, I.M., Troup, C.M., Snellings, W.M., and Ballantyne, B. (1986) 2,4-Pentanedione: 9 -Day and 14-Week Vapor Inhalation Studies in Fischer-344 Rats. Fundam. Appl. Toxicol. 7, 329-339.

(21) Eastman Kodak Comp., HS&HFL No. 79-0359, USEPA New Doc. I.D. 86-920000007 (1979).

(22) Elnabarawy, M.T., Welter, A.N., and Robideau, R.R. (1986) Relative Sensitivity of Three Daphnid Species to Selected Organic and Inorganic Chemicals. Environ. Toxicol. Chem. 5, 393-398.

9. References **Id** 123-54-6
Date 21.05.2003

(23) Frantz, S.W., Ballantyne, B., Leung, H.W. Acute intravenous and inhalation pharmacokinetics of 2,4-pentanedione in the Fischer 344 rat (1998). Industrial Health, 14, 413-428

(24) Garman, R.H., Dodd, D.E., Ballantyne, B. (1995) Central neurotoxicity induced by subchronic exposure to 2,4-pentanedione vapour. Human Experimental Toxicol. 14, 662-671

(25) Gautheron, P., Giroux, J., Cottin, M. et al. (1994) Interlaboratory assessment of the bovine corneal opacity and permeability (BCOP) assay. Toxic in Vitro, 8, 381-392

(26) Gava, C., Perazzolo, M., Zentilin, L., Levis, A.G., Corain, B., Bombi, G.G., Palumbo, M. and Zatta, P. (1989) Genotoxic Potentiality and DNA-Binding Properties of Acetylacetone, Maltol, and Their Aluminium (III) and Chromium (III) Neutral Complexes. Toxicol. Environ. Chem. 22, 149-157.

(27) Gefahrstoffverordnung, 13. Auflage 1999.

(28) Ghose, A.K., and Crippen, G.M. J. Comput. Chem. 7, 565-577, 1986.

(29) Hansch, C., Leo, A., and Joekman, D. (1995) Exploring QSAR - Hydrophobic, Electronic, and Steric Constants. ACS Professional Reference Book, American Chemical Society, Washington, DC.

(30) Katalog wassergefährdender Stoffe (http://www.umweltbundesamt.de/wgs/wgs-index.htm); last update: March 2001.

(31) Kato, F., Araki, A., Nozaki, K. and Matsushima, T. (1989) Mutagenicity of Aldehydes and Ketones. Mutat. Res. 216, 366-367.

(32) Krebs, F., Oekotoxikologische Bewertung von Abwaessern und Umweltchemikalien. Umweltforschungsplan des BMI, Forschungsvorhaben 10205115, Bundesanstalt fuer Gewaesserkunde, Koblenz (1985)

(33) Matsui, S., Yamamoto, R., Yamada, H. (1989) The Bacillus subtilis/microsome rec-assay for the detection of DNA damaging substances which may occur in chlorinated and ozonated waters. Wat. Sci. Tech., 21, 875-887

(34) Mellon Institute of Industrial Research, University of Pittsburgh, Report 31-60 (1968)

(35) Mellon Institute of Industrial Research, University of Pittsburgh, Report 5-7 (1941)

(36) Mellon Institute of Industrial Research, University of Pittsburgh, Report 8-5 (1945)

(37) Misumi, J. et al., Proc. 52nd Congress Jap. Assoc. Ind. Health, 528-529 (1979), (publ. in Japanese)

(38) MITI, Biodegradation and Bioaccumulation-Data of Existing Chemicals based on the CSCL Japan. Ministry of International Trade & Industry (MITI), Japan (1992)

(39) Mount, D.I. and Norberg, T.J. (1984). A Seven Day Life-Cycle Cladoceran Toxicity Test. Environ. Toxicol. Chem. 3, 425-434.

(40) Nacci, D., Jackim, E., and Walsh, R. (1986) Comparative Evaluation of Three Rapid Marine Toxicity Tests: Sea Urchin Early Embryo Growth Test, Sea Urchin Sperm Cell Toxicity Test and Microtox. Environmental Toxicology and Chemistry 5, 521-525.

(41) Nagano, M., Misumi, J., Nomura, S. (1983) An electrophysiological study on peripheral neurotoxicity of 2,3-butanedione, 2,4-pentanedione and 2,5-hexanedione in rats. Jpn. J. Ind. Health, 25, 471-482

(42) Ono, Y., Somiya, I., Kawamura, M. The evaluation of genotoxicity using DNA repairing test for chemicals produced in chlorination and ozonation processes. Wat. Sci. Tech. 23, 329-338 (1991)

9. References **Id** 123-54-6
Date 21.05.2003

(43) RCC-CCR Test Report-No. 671200 (2000): Chromosome Aberration Assay in Mouse Spermatogonia Cells with Acetylacetone.

(44) Safety Data Sheet "Acetylacetone", WACKER Chemie GmbH, 1997.

(45) Schmuck, G., Schlüter, G. (1996) An in vitro model for toxicological investigations of environmental neurotoxins in primary neuronam cell cultures. Toxicol. Industrial Health, 12, 683-695

(46) Sterry, W., and Schmoll, M. (1985) Contact urticaria and dermatitis from self-adhesive pads. Contact Dermat. 13, 284-285.

(47) Syracuse Research Corporation, CHEMFATE Database, http;//esc.syrres.com/scripts/CHFcgi.exe

(48) Thurston, R.V., Gilfoil, T.A., Meyn, E.L., Zajdel, R.K., Aoki, T.I., and Veith, G.D. (1985) Comparative Toxicity of Ten Common Aquatic Species. Water Res. 19, 1145-1155.

(49) Tyl, R.W., Ballantyne, B, Pritts, I.M., Garman, R.H., Fisher, L.C., France, K.A., McNeil, D.J. (1990) An evaluation of the developmental toxicity of 2,4-pentanedione in the Fischer 344 rat by vapour exposure. Toxicol. Ind. Health, 6, 461-474

(50) Tyl, R.W., Ballantyne, B., Fisher, L.C., Tarasi, D.J., Dodd, D.E. (1989) Dominant lethal assay of 2,4-pentanedione vapour in Fischer 344 rats. Toxicology and Industrial Health, 5, 463-477

(51) Union Carbide Corp. Bush Run Research Center, Project Report No. 94U1378, 1995.

(52) Union Carbide Corp. Bushy Run Res. Center, Project Report 49-1, 1986.

(53) Union Carbide Corp. Bushy Run Research Center Project report 48-34, 1985.

(54) Union Carbide Corp. Bushy Run Research Center, Project Report 48-174, 1986.

(55) Union Carbide Corp. Bushy Run Research Center, Project Report 49-20, 1986.

(56) Union Carbide Corp. Bushy Run Research Center, Project Report No. 48-140, 1985.

(57) Union Carbide Corp. Bushy Run Research Center, Project Report No. 48-172, 1986.

(58) Union Carbide Corp. Bushy Run Research Center, Project Report No. 48-4, 1985.

(59) Union Carbide Corp. Bushy Run Research Center, Project Report No. 50-65, 1986.

(60) Union Carbide Corp. Bushy Run Research Center, Project Report No. 53-43, 1990. 2,4-Pentanedione: Bone Marrow Chromosome Aberration Assay in Rats.

(61) Union Carbide Corp. Bushy Run Research Center, Project Report No. 91U0097, 1993.

(62) Union Carbide Corp., Bushy Run Research Center. Project Report No. 94U1423. Export, PA, 1994.

(63) Union Carbide Corporation, Bushy Run Res. Center, Project Report 49-57, 1986.

(64) Union Carbide Corporation. Bushy Run Research Center, Project Report 47-132, 1984.

(65) Union Carbide Corporation. Bushy Run Research Center, Project Report No. 49-124, 1986.

(66) Union Carbide Corporation. Material Safety Data Sheet "2,4-Pentanedione".

(67) Union Carbide Corporation: Bushy Run Research Center, Project Report No. 93U1254, 1994.

9. References **Id** 123-54-6
Date 21.05.2003

(68) USEPA, Draft Report- the joint action of multiple organic toxicants on the Fathead Minnow, New Doc. I.D. 40-83421321 (1986)

(69) Wacker-Chemie, Abwasserbericht 1965, Werk Burghausen, 36-39 (1965)

(70) Zimmermann, F.K., Mayer, V.W., Scheel, I., Resnick, M.A. (1985) Acetone, methyl ethyl ketone, ethyl acetate, acetonitrile and other polar aprotic solvents are strong inducers of aneuploidy in Saccharomyces cerevisiae. Mutat. Res., 149, 339-351

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT