Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Toluenesulfonamides

Evaluation statement

14 January 2022

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AICIS evaluation statement

Subject of the evaluation

Toluenesulfonamides

Chemicals in this evaluation

Name	CAS registry number
Benzenesulfonamide, 2-methyl-	88-19-7
Benzenesulfonamide, ar-methyl-	1333-07-9
Benzenesulfonamide, 4-methyl-	70-55-3

Reason for the evaluation

The Evaluation Selection Analysis indicated a potential risk to human health.

Parameters of evaluation

Chemicals in this group are ortho and para (*o*- and *p-)* isomers of toluenesulfonamide, listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation will focus on determining whether the identified health hazards for these chemicals are appropriately risk–managed for the range of reported industrial uses.

The chemicals in this evaluation will be referred to as follows:

- CAS No. 88-19-7 will be referred to as *o*-toluenesulfonamide
- CAS No. 70-55-3 will be referred to as *p*-toluenesulfonamide
- CAS No. 1333-07-9 will be referred to as toluenesulfonamide

Note that related information may be found under the alternative spelling, that is, toluenesulphonamides.

Summary of evaluation

Summary of introduction, use and end use

Toluenesulfonamides are reported internationally to be used in cosmetic nail polish products at concentrations of up to 10%. The mixture of *o*- and *p*-toluenesulfonamide, or *p*-toluenesulfonamide alone, is reported to be used in the formulation of toluenesulfonamide-formaldehyde resin for fingernail polishes and enamels (Government of Canada 2017; NTP 2002).

Both *o*- and *p*-toluenesulfonamides are reported to be used internationally in paint and coating products, inks and toners, and in adhesives and sealants (REACHa; REACHb; OECD 2000; US CDR 2016). The mixture of *o*- and *p*-toluenesulfonamide is also reported to be used as a chemical intermediate for fluorescent pigments and as a plasticiser (OECD 2002).

A group entry for 'sulfonamides' is included in Schedule 4 (S4) of the Poisons Standard – The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP 2021). As toluenesulfonamides are not separately specified in the Poisons Standard, this generic listing for sulfonamides is expected to apply to the chemicals in this evaluation, by default. There is no exemption from this scheduling entry for industrial uses. Given this scheduling was based on recommendations regarding antibiotic resistance (JETACAR 1999), and the range of reported industrial uses of toluenesulfonamides overseas, it is considered likely that introducers would not readily identify that this non–specific Schedule 4 entry applies to the industrial use of these chemicals.

Human health

Summary of health hazards

The critical health effects for risk characterisation of this group of chemicals is potential repeated dose toxicity.

While there is insufficient data to meet classification criteria, the lowest NOAEL (no observed adverse effect level) for toluenesulfonamides in rats, was reported to be 20 mg/kg body weight (bw)/day, based on clinical signs of toxicity and effects in the liver and bladder reported in male and female rats at doses of greater than or equal to 100 mg/kg bw/day (REACHa; REACHb; OECD 1993; OECD 2002).

Based on the available data, toluenesulfonamides are also:

- expected to have low acute oral, dermal and inhalation toxicity
- expected to be at most to cause slight skin and eye irritation
- not expected to cause skin sensitisation
- not expected to be genotoxic
- not expected to be carcinogenic
- not expected to not cause specific reproductive or developmental toxicity.

Further details on the evaluation of these health hazards is provided in the **Supporting Information**.

Health hazard classification

These chemicals do not satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety. This evaluation does not consider classification of physical hazards.

Summary of health risk

Public

Current regulatory controls in Australia, in effect, preclude the industrial use of the chemicals in this group (refer to **Supporting information**). However, the chemicals are reported internationally to be present in cosmetic (nail polish) and domestic (paints and coatings) products.

While incidental dermal and ocular exposure to toluenesulfonamides may occur from use of paints and coating products containing the chemicals, intentional topical application is required during normal use of cosmetic nail polish products; therefore, dermal exposure to toluenesulfonamdies is expected to be significantly higher for this use type.

Assessment of the margin of exposure (MOE) for use of toluenesulfonamides in nail polish products, comparing estimated dermal exposure levels with the NOAEL of 20 mg/kg bw/day, gives MOEs of greater than 100. These MOEs indicate a low risk of adverse health effects occurring due to use of the chemicals in nail polish at reported concentration levels (refer to **Human health risk characterisation** section).

Workers

During product formulation and packaging, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Based on the hazard profile, the chemicals are unlikely to pose a risk to workers although systemic long–term effects may occur following repeated exposure to high doses of the chemicals.

Conclusions

The conclusions of this evaluation are based on the information described in the statement. Obligations to report additional information about hazards under section 100 of the *Industrial Chemicals Act 2019* apply.

The Executive Director is satisfied that the identified human health risks can be managed within the existing risk management frameworks. This is provided that all requirements are met under environmental, workplace health and safety and poisons legislation, as adopted by the relevant state or territory. The proposed means of managing the risks identified during this evaluation are set out in the **Recommendations** section.

Recommendations

Public health

Recommendation to Department of Health

It is recommended that the delegate of the Secretary for Poisons Scheduling refine the current SULFONAMIDES entry in the Poisons Standard, noting:

- the chemicals in this assessment have widespread industrial use, for example in the manufacture of resins
- these chemicals do not have therapeutic use
- there are close to 300 listings on the Inventory described as “sulfonamide” as part of the CAS name – these cover a wide range of chemistry and of uses, including saccharin and the sulfonamides of perfluorooctanesulfonic acid (PFOS)
- only a more limited subclass has antibiotic activity
- international restrictions referring to sulfonamides specify these as derivatives of sulfanilamide.

Workers

Information on managing identified risks

The information in this report should be used by a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) to determine the appropriate controls under the Model Work Health and Safety Regulations.

Control measures that could be implemented to manage the risk arising from dermal and inhalation exposure to these chemicals include, but are not limited to:

- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

Measures required to eliminate, or manage risk arising from storing, handling and using a hazardous chemicals depend on the physical form and how the chemicals are used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker’s health.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

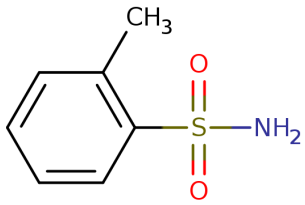
Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

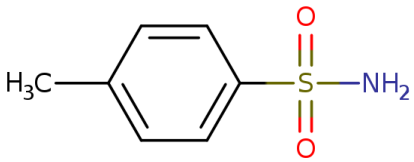
Supporting information

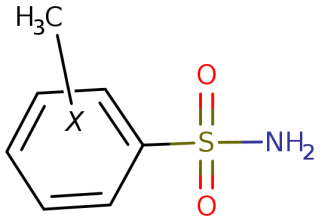
Grouping rationale

This group consists of the *ortho* and *para* (*o*- and *p*-) isomers of toluenesulfonamide. These can also be described as benzenesulfonamides with a methyl group attached at the 2 position (*ortho*), or at the 4 position (*para*). The chemical listed under CAS No. 1333-07-9 has also been included in this group, as it is reported to be the mixture of these two isomers (REACHc).

Chemical identity

Chemical name	Benzenesulfonamide, 2-methyl-
CAS number	88-19-7
Synonyms	*o*-toluenesulfonamide; 2-methylbenzenesulfonamide; toluene-2-sulphonamide
Structural formula	
Molecular formula	C7H9NO2S
Molecular weight (g/mol)	171.22
SMILES	Cc1ccccc1S(N)(=O)=O
Chemical description	Refer to **Grouping rationale**.

Chemical name	Benzenesulfonamide, 4-methyl-
CAS number	70-55-3
Synonyms	*p*-toluenesulfonamide; 4-tosylamide 4-methylbenzenesulfonamide; toluene-4-sulphonamide
Structural formula	
Molecular formula	C7H9NO2S
Molecular weight (g/mol)	171.22
SMILES	Cc1ccc(cc1)S(N)(=O)=O
Chemical description	Refer to **Grouping rationale**

Chemical name	Benzenesulfonamide, ar-methyl-
CAS number	1333-07-9
Synonyms	toluenesulfonamide; ar-toluenesulfonamide; o, *p*-toluenesulfonamide; Tosylamide
Structural formula	
Molecular formula	C7H9NO2S
Molecular weight (g/mol)	171.22
SMILES	N/A
Chemical description	The mixture of o- and *p*-toluenesulfonamide (refer to **Grouping rationale**).

Relevant physical and chemical properties

The chemicals in this group are all white to creamy organic crystalline solids at room temperature, with low odour. Water solubilities for these chemicals range from 1.6 to 5.1 g/L at 25°C, and vapour pressures range from 6.6×10^{-5} to 2.86×10^{-4} Pa at temperatures of 20–25°C (REACHa, REACHb, REACHc).

Existing Australian regulatory controls

AICIS

There are no AICIS-specific regulatory controls applicable to the chemicals in this group.

Public

No specific regulatory controls apply to toluenesulfonamides, or the individual chemicals in this group. However, a group entry for 'sulfonamides', is included in Schedule 4 of the Poisons Standard (SUSMP 2021), as described below.

Schedule 4:

'SULFONAMIDES **except**:

a) when separately specified in this Schedule;
b) when included in Schedule 3, 5 or 6; or
c) when packed and labelled solely for use as a herbicide.'

It should be noted that inclusion of sulfonamides in the schedules of the Poisons Standard was based on the antimicrobial properties of sulfonamides, and identified therapeutic and agricultural uses; specifically, in consideration of Recommendation 6 of the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) report in 1999, which recommended 'that all antibiotics for use in humans and animals (including fish) be classified as S4 (prescription only)' (JETACAR 1999; NDPSC 2004; NRA 2000).'

There is no indication that industrial uses of sulfonamides were considered in determining this scheduling entry. There is also no exemption from this scheduling entry for industrial uses, as the Poisons Standard states that 'Poisons which are packed and sold solely for industrial, manufacturing, laboratory or dispensary use are exempt from all labelling requirements included in the SUSMP as they are covered by labelling requirements under applicable jurisdictional Work Health and Safety laws, as amended from time to time. Note, however that this exemption does not extend to controls on supply of these poisons.'

As toluenesulfonamides are not separately specified in the Poisons Standard, this generic listing for sulfonamides is expected to apply to the chemicals in this evaluation, by default.

Schedule 4 (S4) chemicals are described as, 'Substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription.' S4 chemicals are labelled with 'Prescription Only Medicine' or 'Prescription Animal Remedy'.

Workers

The chemicals in this group are not listed on the Hazardous Chemical Information System (HCIS) and no specific exposure standards are available in Australia (Safe Work Australia).

International regulatory status

Other

Cosmetic use

Unless specified otherwise, toluenesulfonamides are covered by regulatory controls for sulfonamides. However, many restrictions referring to sulfonamides specify these as derivatives of sulfanilamide, thereby excluding toluensulfonamides from those restrictions.

An example of this, is the listing of 'Sulphonamides (sulphanilamide and its derivatives obtained by substitution of one or more H-atoms of the -NH2 groups) and their salts', which is included in, but not limited to, the following:

- EU Regulation (EC) No 1223/2009 on cosmetic products, Annex II – List of substances prohibited in cosmetic products (EU 2021)
- New Zealand cosmetic products Group Standard – Schedule 4, table 1 – Components cosmetic products must not contain (NZ EPA 2020)
- Chile Cosmetic Control, National system regulation – List of substances which must not form part of the composition of cosmetic products (Galleria Chemica)
- China Ministry of Health, Hygienic standard for cosmetics – List of banned substances for use in cosmetics (Galleria Chemica)
- Philippines Restricted ingredients for use in cosmetics – List of substances which must not form part of the composition of cosmetic products (Galleria Chemica)

- Saudi Arabia Food & Drug Authority – List of substances prohibited in cosmetic products (Galleria Chemica).

While the Canadian Cosmetic Ingredient Hotlist – List of ingredients that are prohibited for use in cosmetic products (Canadian Cosmetic Ingredient Hotlist 2019) lists, 'Sulfonamides and their salts obtained by substitution of one or more H-atoms of the -NH2 groups', it also provides representative CAS numbers for this listing, all of which are derivatives of sulfanilamide.

The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II, Part 1 – List of substances which must not form part of the composition of cosmetic products (ACD 2020) does not use the generic sulfonamides reference in its listing of 'Sulphanilamide and its derivatives obtained by substitution of one or more H-atoms of the -NH2 groups, and their salts'.

The European Commission Cosmetic Ingredient and Substances (CosIng) database includes the following specific listings:

- 'TOSYLAMIDE' under the CAS No's. 70-55-3 and 88-19-7, with reference to Annex II of (EC) 2009/1223
- '4-TOSYLAMIDE' under CAS No. 70-55-3, without reference to Annex II of (EC) 2009/1223.

Exposure Standards

No specific international exposure standards have been identified for the chemicals in this group.

Health hazard information

Toxicokinetics

Following oral administration of *o*-toluenesulfonamide in rats, the chemical is reported to be rapidly absorbed and then eliminated mostly via urine (approximately 90% within 24 hours), with only minimal excretion via faeces (approximately 5%). Excretion in urine is reported to be comparatively slower in humans (OECD 2002; REACHa). In both rats and humans, the main metabolites detected were 2-sulfamoylbenzyl alcohol and its sulphate and glucuronic acid conjugates. Saccharin was also detected as a metabolite in urine, more predominantly in humans.

Similar to the o-isomer, *p*-toluenesulfonamide was reported to be rapidly absorbed and subsequently eliminated, mostly via urine, following oral administration of the chemical in rats (REACHb; NTP 2016). While human data are unavailable, similar results were reported in dogs. The main metabolites detected were 4-sulfamoylbenzoic acid, 4-sulfamoylbenzyl alcohol and 4-sulfamoylbenzaldehyde.

While dermal absorptions studies using toluenesulfonamides are not available, data from studies using sodium *p*-toluenesulfonchloramide (also referred to as chloramine-T), are considered appropriate for read-across; chloramine-T has been demonstrated to rapidly and almost exclusively be converted to *p*-toluenesulfonamide following absorption (REACHc; REACHd; NTP 2016). In in vitro studies, >99% of chloramine-T was reported to be converted to *p*-toluenesulfonamide within 2 minutes of contact with rat stomach and intestinal content.

In an in vitro dermal absorption study using human skin, approximately 12% of a 0.5% chloramine-T solution was reported to pass the skin completely, with about 8% of the applied dose passing the stratum corneum but remaining fixed in the skin after 24 hours. The highest dermal absorption level was reported to be approximately 20%, with the level of absorption inversely proportionate with dose concentration level. For a 3% chloramine-T solution, the total dermal absorption level was reported to be approximately 10%, (REACHd). The rapid degradation of chloramine-T to *p*-toluenesulfonamide was reported to result in only *p*-toluenesulfonamide passing the skin. Therefore, a conservative dermal absorption level of 20% is considered applicable to *p*-toluenesulfonamide.

Acute toxicity

Oral

Oral median lethal dose (LD50) values in rats for the chemicals in this group are reported to be >2000 mg/kg bw (REACHa; REACHb; REACHc; OECD 1993; OECD 2002; NTP 2016). While a comparatively higher mortality rate was reported in females administered either *o*- or *p*-toluenesulfonamide at 2000 mg/kg bw/day, there is insufficient evidence to establish a lower female-specific LD50 for toluenesulfonamides.

Dermal

The dermal LD50 values for *o*-toluenesulfonamide and for a mixture of the o- and *p*-toluenesulfonamides (3:7 ratio), are each reported to be >2000 mg/kg bw (REACHa; REACHb; REACHc). No data are available for *p*-toluenesulfonamide alone.

Inhalation

No specific toxicity data are available.

Corrosion/Irritation

Skin irritation

Based on the limited available information, the chemicals are reported to cause slight skin irritation in animal studies but are not classifiable as skin irritants.

In skin irritation studies conducted similar to the Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 404, 0.5 mg of either *o*-toluenesulfonamide, *p*-toluenesulfonamide or a mixture of o- and *p*-toluenesulfonamides was applied to the intact or abraded skin of New Zealand White (NZW) rabbits (n=6) under occlusive conditions, for an exposure period of 24 hours (REACHa; REACHb; REACHc). The skin was evaluated at 24 and 72 hours after initial application of the chemicals. While no oedema formation was observed, slight erythema was reported (mean score of 0.6 out of 4), which was not reversible at 72 hours. The study observation period did not extend beyond 72 hours.

Eye irritation

Based on the limited available information, the chemicals are reported to cause slight eye irritation in animal studies but are not classifiable as eye irritants.

In eye irritation studies conducted similar to OECD TG 405, 0.1 g of either *o*-toluenesulfonamide, *p*-toluenesulfonamide or a mixture of o- and *p*-toluenesulfonamides was instilled into one eye each of 6 NZW rabbits, with the other eye serving as an untreated control (REACHa; REACHb; REACHc). The eyes were not irrigated after application. Examinations of the eyes were conducted at 24, 48 and 72 hours, and at the end of the 7–day study observation period. Slight corneal opacity (mean score of 0.1 out of 4), iritis (mean score of 0.05 out of 2), and chemosis (mean score of 0.4 out of 4) were observed and all reported to be fully reversible within 72 hours. Conjunctival redness (mean score of 1.05 out of 3) was not fully reversible in 3 out of 6 animals by the end of the 7–day observation period. The observation period did not extend to 21 days to study reversibility. However, as mean scores per animal for conjunctival redness were not ≥2, the criteria for classification are not met.

Sensitisation

Skin sensitisation

Based on the available information, *p*-toluenesulfonamide is not classifiable as a skin sensitiser.

In a local lymph node assay (LLNA) conducted in accordance with OECD TG 429, 25 µL of *p*-toluenesulfonamide was applied to the dorsal surface of the ears of female CBA mice (4 animals/dose) at dose concentrations of 10, 25 or 50% (w/v) in an acetone/olive oil vehicle, for 3 consecutive days (REACHb). No local irritation effects or clinical signs of toxicity were observed, and mean stimulation indices (SI) were reported to be <3 for all concentrations (SI values of 2.97, 1.48 and 1.23, respectively). Therefore, under the conditions of the study, the chemical did not induce skin sensitising effects at concentrations up to 50%.

No data are available for *o*-toluenesulfonamide.

Repeat dose toxicity

Oral

Several repeated oral exposure studies are available, with the lowest NOAEL in rats reported to be 20 mg/kg bw/day, based on clinical signs of toxicity and effects in the liver, following exposure to *o*-toluenesulfonamide. At 100 mg/kg bw/day and above, effects on the bladder (hyperplasia or thickening of the urinary bladder epithelium) have also been reported in male and female rats following repeated exposure to toluenesulfonamides. While there is insufficient data to meet classification criteria, the NOAEL value is supported by these observations.

In a combined repeated dose and reproductive/developmental toxicity study (conducted in accordance with OECD TG 422), *o*-toluenesulfonamide was administered by oral gavage to Sprague Dawley (SD) rats (13 animals/sex/dose) at 20, 100 or 500 mg/kg bw/day. Males were treated for 42 days, and females treated from 14 days before mating, to day 3 of lactation (REACHa; OECD 2002). Clinical signs of toxicity (decreased motor activity, increased salivation and incidence of animals in prone position) and significantly reduced body weights were observed in both sexes at doses greater than or equal to 100 mg/kg bw/day, with 5 mortalities observed in females only from the 500 mg/kg bw/day group, on days 3 to 5 of treatment. Histopathological observations included treatment related effects in

the liver of both males and females at >20 mg/kg bw/day. This included hypertrophy of the centrilobular hepatocytes and a dose dependent, statistically significant ($p<0.01$) incidence of cytoplasm reported as having a 'ground glass' appearance. Hyperplasia of the urinary bladder epithelium was also reported in one male at 100 mg/kg bw/day and 2 males at 500 mg/kg bw/day, while an increased incidence of involution of the thymus (atrophy) was reported in females from the 500 mg/kg bw/day group in comparison to the control group (statistical significance). A NOAEL of 20 mg/kg bw/day was established based on clinical signs and histopathological changes in liver seen at higher doses.

In a combined repeated dose and reproductive/developmental toxicity study using *p*-toluenesulfonamide (conducted in accordance with OECD TG 422), the chemical was administered by oral gavage to SD rats (13 animals/sex/dose) at 120, 300 or 750 mg/kg bw/day, with males treated for 42 days, and females treated from 14 days before mating, up to day 3 of lactation (REACHb; OECD 1993). A dose dependent increase in the number of hypersalivating animals was observed in both males and females across all dose groups. Haematuria (blood in urine) was also reported in 4 males from the 750 mg/kg bw/day group, one to 2 days after commencement of treatment. No mortalities were observed. However, reduced body weights in males at 750 mg/kg bw/day and in females at doses greater than or equal to 300 mg/kg bw/day were reported, with statistical significance only at the highest dose.

In the same study histopathological observations included: involution of the thymus noted in 8 females and 2 males from the high dose group; 3 females from the mid dose group and one female from the control group. Decreased thymus weights (statistical significance not indicated) were also reported in both sexes at 750 mg/kg bw/day and in females at 300 mg/kg bw/day. Reported effects on the liver included slightly increased relative liver weights, and 'dark–coloured' livers in 6 male animals from the high dose group (OECD 1993). On histopathology, foci of necrosis were reported in one male and one female from the high dose group, and in one female from the low dose group. In the high–dose female, fatty change was observed in the entire hepatic lobule. Areas of fatty change in the hepatic lobule were reported in animals across all treatment groups; however, no dose dependent trend was identified. While microgranluoma was observed in all treatment groups, no significant difference in frequency and degree from the control group was reported for male animals. It was unclear if this is also the case for female animals from this study (REACHb). Effects on the bladder included thickening of the urinary bladder epithelium in both males and females across all treatment groups: 18 animals (11 males and 7 females) from the high dose group, 23 animals (11 males and 12 females) from the mid dose group, and 7 animals (6 males and one female) from the low dose group. No effects on the bladder were reported for control group animals. A NOAEL could not be established for this study due to clinical signs and histopathological change in the urinary bladder seen across all the dose groups.

Details from the two studies above are also presented in the **Reproductive and developmental toxicity** section.

In a 90–day repeated oral dose toxicity study, conducted in accordance with OECD TG 408, p-toluenesulfonamide was incorporated into the diet of Wistar rats (10 animals/sex/dose), at nominal concentrations of 1000, 3000 or 10000 ppm. Average actual doses administered to the rats were reported to be equivalent to 70, 214 and 738 mg/kg bw/day for males, and 80,248 and 795 mg/kg bw/day for females (REACH b; NTP 2016). While limited study details are available, NOAEL values of 214 mg/kg bw/day for males and 248 mg/kg bw/day for females were reported, based on significantly reduced body weights in high dose group animals, with hyperplasia of the urinary bladder epithelium also reported in 2 males at the highest dose.

In other available studies, p-toluenesulfonamide was incorporated into the diet of F344/NTac rats and B6C3F1/N mice, 5 days per week for 90 days (REACHb). NOAELs of 200 and 210 mg/kg bw/day were reported for male and female rats, while NOAEL values of 420 and 380 mg/kg bw/day were reported for male and female mice, respectively, based on reduced body weights at higher doses.

Dermal

No available data have been identified.

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, toluenesulfonamides are not expected to be genotoxic.

For *o*-toluenesulfonamide, negative genotoxicity results were reported in bacterial and mammalian cell in vitro assays (REACHa), as listed below:

- An in vitro bacterial reverse mutation assay at 1–1000 µg/plate, with or without metabolic activation, in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100, and in *Saccharomyces cerevisiae.*
- An in vitro mammalian cell gene mutation assay in mouse lymphoma L5178Y cells at 253–1712 µg/mL, with or without metabolic activation.
- An in vitro mammalian chromosomal aberration assay in Chinese hamster lung (CHL/IU) cells, at 375–3000 µg/mL, with or without metabolic activation.

In an in vitro mammalian cell gene mutation assay, in mouse lymphoma L5178Y cells (conducted according to OECD TG 476) at 125-2000 µg/mL, *p*-toluenesulfonamide induced a positive response at the highest dose only, with metabolic activation; however, this dose was also reported to be cytotoxic. Negative responses were reported at all doses without metabolic activation.

Negative results for the chemical *p*-toluenesulfonamide were reported in 4 in vitro assays and 2 in vivo assays (REACHb; NTP 2016), as listed below:

- An in vitro bacterial reverse mutation assay (similar to OECD TG 471) at 1–1000 µg/plate, with or without metabolic activation, in *S. typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100, and in *S. cerevisiae.*
- An in vitro bacterial reverse mutation assay (according to OECD TG 471) at 50–5000 µg/plate, with or without metabolic activation, in *S. typhimurium* TA 1535, TA 1537, TA 98, TA 100 and *Escherichia coli* WP2.
- An in vitro point mutation assay (Ames test) at 33–10000 µg/plate, in *S. typhimurium* strains TA100, TA98 and TA102, with or without metabolic activation.
- An in vitro mammalian chromosomal aberration assay in Chinese hamster lung fibroblasts (V79), at 0.33–1.7 mg/mL, with or without metabolic activation.
- In two in vivo chromosomal aberration (micronucleus) assays in Crl:CD-1 (ICR) mice, following administration of the chemical by oral gavage at 80–1,500 mg/kg bw. While clinical signs of toxicity were observed in treated animals, no cytotoxicity was reported (REACH b).

The mixture of o- and *p*-toluenesulfonamide was also reported to be negative for genotoxicity in two in vitro bacterial reverse mutation assays (similar to OECD TG 471) in *S. typhimurium*

strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100, and in *S. cerevisiae,* at concentrations of 1–1000 µg/plate, with or without metabolic activation (REACHc).

Carcinogenicity

Based on the available information, the chemicals are not expected to be carcinogenic. Low incidence of benign urinary bladder tumours in male and female SD rats have been reported in two separate long-term feeding studies using *o*-toluenesulfonamide. However, neither study reported the incidence to be statistically significant or dose dependent.

In a two–generation lifetime feeding study, SD rats (50 animals/sex/dose) were fed *o*-toluenesulfonamide at concentrations of 2.5, 25 or 250 mg/kg bw/day in diet (OECD 2002; REACHa). First generation (F0) animals were treated for 142 weeks (from 90 days prior to mating), while second generation (F1) animals were treated for 127 weeks (after weaning). Benign urinary bladder tumours were reported in F0 animals from the control group (one male), the 2.5 mg/kg bw/day group (one male and one female) and the 250 mg/kg bw/day groups (one male), and in two F1 females from the 2.5 mg/kg bw/day group. However, the incidence was neither statistically significant nor dose dependent. Other non-neoplastic lesions were reported in the lung, liver and spleen of treatment group animals; however, no statistical significance, or clear dose–dependency were demonstrated. A significant difference ($p < 0.05$) in the growth curve of male and female animals from the highest dose group compared with controls, was reported; no further details are available. No treatment related effects on long-term survival were reported for this study.

In a one–generation lifetime feeding study, of limited reliability, *o*-toluenesulfonamide was fed to male and female SD rats at 20 and 200 mg/kg bw/day (76 animals/group), commencing from 3 months of age (OECD 2002; REACHa). Urinary bladder carcinoma was reported in one animal from the 200 mg/kg bw/day group, urinary bladder papillomas were reported in 3 animals from the 20 mg/kg bw/day group and in 4 animals from the 200 mg/kg bw/day group. No tumours were reported in control group animals. Only limited study details are available, with no information on the sexes of animals with bladder tumours, or the presence or absence of bladder parasites. No treatment related effects on long-term survival were reported for this study.

In two studies of limited reliability, *o*-toluenesulfonamide was reported to not induce changes in the incidence of tumours in female Wistar rats following exposure to chemical at 70 mg/kg bw/day in drinking water (n=63), or at 79 mg/kg bw/day in diet (n=53), daily, for 2 years. No further study details are available (OECD 2002; REACHa).

Reproductive and development toxicity

Based on the available information, toluenesulfonamides are not considered to be specific reproductive toxins. Studies in rats reported significantly reduced body weights of pups following maternal exposure to the chemicals; however, this was only observed at doses that were also toxic to the parental animals.

In a two–generation reproductive toxicity study, conducted in accordance with OECD TG 416, *p*-toluenesulfonamide was fed to Wistar rats (24 animals/sex/dose) at nominal dose concentrations of 1000 ppm (actual intake of 52–78 mg/kg bw/day for males and 75–161 mg/kg bw/day for females), 3000 ppm (actual intake of 165 –237 mg/kg bw/day for males and 232–99 mg/kg bw/day for females) or 10000 ppm (566–832 mg/kg bw/day for males and 733–1631 mg/kg bw/day for females), in diet (REACHb). F0 and F1 animals were treated for 10 weeks prior to mating until euthanised. A NOAEL of 1000 ppm for parental toxicity and a NOAEL of 3000 ppm for developmental toxicity, were established based on

statistically significant decreased body weights at higher dose levels. No treatment related reproductive effects were reported for this study.

In a prenatal developmental toxicity study (OECD TG 414, with deviations), toluenesulfonamide (a mixture of 32% *o*- isomer and 68% *p*- isomer), was administered to pregnant female rats (COBS CD strain; 25 animals/dose) by oral gavage, at 50, 250 or 500 mg/kg bw/day, from day 6 to day 15 of gestation (REACHc). No mortalities, or clinical signs of toxicity were reported in any of the treatment groups. Statistically significant reductions in maternal body weight, and reduced foetal body weights, were reported at >50 mg/kg bw/day. Increased incidence of post-implantation loss was reported at >50 mg/kg bw/day, with statistical significance only at the highest dose. At the highest dose, an increased number of litters with pups exhibiting unossified sternebrae was also reported. No other treatment related developmental or morphological abnormalities in offspring were reported.

Details from the studies below are also presented in the **Repeat dose toxicity** section.

In a combined repeated dose and reproductive/developmental toxicity study (conducted in accordance with OECD TG 422), *o*-toluenesulfonamide was administered by oral gavage to SD rats (13 animals/sex/dose) at 20, 100 or 500 mg/kg bw/day; males were treated for 42 days, and females treated from 14 days before mating, up to day 3 of lactation (REACHa; OECD 2002). No details are available on the exposure period in males prior to mating. Clinical signs of toxicity and significantly reduced body weights were observed in male and female parental animals at doses greater than or equal to 100 mg/kg bw/day, with 5 mortalities observed in females only from the 500 mg/kg bw/day group. No treatment related morphological abnormalities in offspring were reported. However, a significant reduction in the body weights of pups on days zero and 4 of lactation ($p<0.05$ and $p<0.01$, respectively), was reported for animals from the 500 mg/kg bw/day maternal dose group. A NOAEL of 100 mg/kg/day for both reproductive and developmental toxicity was reported for this study, while a NOAEL of 20 mg/kg bw/day for parental toxicity was established based on clinical signs and histopathological change in liver seen at higher doses.

In a combined repeated dose and reproductive/developmental toxicity study (conducted in accordance with OECD TG 422), *p*-toluenesulfonamide was administered by oral gavage to SD rats (13 animals/sex/dose) at 120, 300 or 750 mg/kg bw/day, with males treated for 42 days, and females treated from 14 days before mating, to day 3 of lactation (REACHb; OECD 1993); the exposure period pf 42 days in males is reported to have occurred prior to mating (NTP, 2016). Clinical signs of toxicity (hypersalivation) were observed in parental animals from all treatment groups; at the highest dose, haematuria was reported in 4 males at one to 2 days after commencement of treatment. While no mortality was observed, reduced body weights in males at 750 mg/kg bw/day and in females at doses greater than or equal to 300 mg/kg bw/day were reported, with statistical significance only at the highest dose. Newborn pup body weights and the survival rate were also reported to be significantly decreased at the highest dose; however, no significant difference was observed in pups at day 4 of lactation. No treatment related morphological abnormalities in offspring were reported for any of the treatment groups. A NOAEL of 300 mg/kg bw/day for reproductive toxicity was reported for this study, while a NOAEL of <120 mg/kg bw/day is likely for parental toxicity based on clinical signs and histopathological change in the urinary bladder seen at higher doses.

Human health risk characterisation

Critical health effects

The critical health effects for risk characterisation of this group of chemicals is potential repeated dose toxicity. While there is insufficient data to meet classification criteria, clinical signs of toxicity and effects in the liver and bladder are reported in male and female rats following repeated exposure to toluenesulfonamides at doses of greater than or equal to 100 mg/kg bw/day. These study results are sufficient to set a repeated dose toxicity NOAEL of 20 mg/kg bw/day (refer to **Repeat dose toxicity** section).

Public risk

Considering the types of consumer products (domestic and cosmetic) identified as containing toluenesulfonamides (refer to **Summary of introduction, use and end use** section), the main route of exposure is expected to be through the skin.

In a 2017 Canadian quantitative risk assessment of *o*-toluenesulfonamide, a repeat dose toxicity NOAEL range of 20 to 25 mg/kg bw/day was used as the critical effect level in determining risk to human health from use of cosmetic nail polish products containing the chemical (Government of Canada 2017). Based on an estimated dermal exposure level of 7.1×10^{-3} mg/kg bw per application, the Canadian report determined the margin of exposure (MOE) to be much greater than 100, indicating a low risk of adverse health effects due to use of *o*-toluenesulfonamide at 5% in nail polish.

The calculated MOE was derived using an assumed 20% dermal absorption level, based on data for chloramine-T, which is considered an appropriate read–across chemical for this purpose (refer to **Toxicokinetics** section).

It should be noted that nail polish products identified were reported to contain both *o*- and *p*-toluenesulfonamides at 5% each (Canadian Government 2017), bringing the total concentration of toluenesulfonamides to 10%. Applying the lowest repeat dose toxicity NOAEL of 20 mg/kg bw/day as the critical effect level for determining risk for this group of chemicals still results in an MOE of much greater than 100.

This indicates that the risk of potential repeated dose toxicity from the use of nail polish products containing toluenesulfonamides, likely to be available to consumers, is low.

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