WCSR Advice 2015-02

SCIENTIFIC COMMITTEE REACH (WCSR)

ADVICE ON TOXICOKINETICS OF 2-ETHYLHEXYL ACETATE

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Context

The Belgian Competent Authority requested an advice to support the decision making process for the substance evaluation of 2-ethylhexyl acetate, as defined in the article 44 of the REACH Regulation. The Belgian Competent Authority has been appointed by ECHA (European Chemicals Agency) to evaluate this substance in 2015. The Belgian Competent Authority will need to finalize the evaluation (draft) by the end of 2015.

Substance Identity

Public Name: 2-ethylhexyl acetate

EC Number(s): 203-079-1

CAS Number(s): 103-09-3

Structural formula:

Concern

The concern is that the registrant applied read-across throughout his dossier with 2-ethylhexanol (CAS 104-76-7). However there is no quantitative information on the potential metabolite 2-ethylhexanol which is used for read-across for several human health endpoints. Can the read-across from 2-ethylhexyl acetate to 2-ethylhexanol be accepted (considered plausible), or is further information needed? Can the test results with the alcohol be used for the evaluation of the acetate?

ANALYSIS OF AVAILABLE INFORMATION

A. Toxicokinetics of 2-ethylhexyl acetate

Absorption

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food has written an opinion on 2-ethylhexyl derivatives, which are used as flavourings (EFSA, 2008). The experts state that 2-ethylhexyl acetate is hydrolysed in the gastrointestinal tract (GI) tract prior to absorption but that there is no experimental evidence for this.

COSMOS-SkinPermPred model predicts the skin permeability coefficient (Kp) for organic compounds, based on the calculated molecular volume and octanol-water partition coefficient (Kow). The predicted Kp of 2-ethylhexyl acetate is 0.0206 cm/hr. The Dermwin model uses the molecular weight and the log Kow to estimate the Kp for compounds in water. The estimated Kp is 0,0515 cm/hr (Dermwin v.2.02).

Metabolism

Experts within various fora state that in general, aliphatic linear and branched-chain esters of aliphatic linear saturated carboxylic acids are anticipated to be readily hydrolysed in humans to their component alcohols and carboxylic acids (IPCS 40; JECFA, 1998; HSDB, 1995). The chemical reaction is given in Figure 1 (from JECFA, 1998).

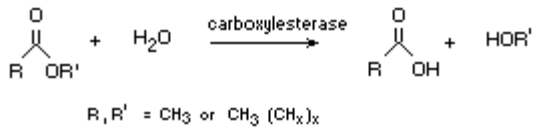


Figure 1. Hydrolysis of esters in mammals

The rat liver S9 metabolism simulator in the OECD (Q)SAR Toolbox (v.3.3) gives 4 potential metabolites for 2-ethylhexyl acetate. The metabolites proposed by the model are: 2-ethylhexanol, acetic acid, 2-ethylhexanal, and 2-ethylhexanoic acid. The estimated toxic hazard classification of the four substances is low (Cramer class I). The HSDB database states that ethylhexanol has the same relative low degree of toxicity as 2-ethylhexyl acetate (HSDB, 1995).

No estimation is given by the toolbox of the time needed for the metabolisation of 2-ethylhexyl acetate.

The rapid and complete hydrolysis of the acetate esters of simple primary alcohols have been demonstrated for methyl, ethyl, butyl, isobutyl, pentyl and isopentyl alkyl esters and has been

demonstrated to occur for the acetate ester of 2-ethylhexanol as well. The hydrolysis reaction occurs in the gut, respiratory tissue, and skin thereby allowing the corresponding alcohol to be absorbed into the systemic circulation (SIAM, 2010). The OECD SIAM task force who evaluated 2-ethylhexyl acetate states that acetate esters of primary alcohols undergo rapid hydrolysis; the reaction is catalysed by esterases and proteases found in mammalian tissues and gastric fluids (SIAM, 2010). The rapid and complete hydrolysis of 2-ethylhexyl acetate to 2-ethylhexanol as primary metabolite has been demonstrated to occur *in vitro* and *in vivo*. Deisinger (2005) demonstrated the initial hydrolysis reaction in an *in vitro* experiment using rat blood. 2-Ethylhexanol was formed *in vitro* within blood in a concentration and time-dependent manner from the administered 2-ethylhexyl acetate. The half-life for metabolism of 2-ethylhexyl acetate to 2-ethylhexanol was 2.3 minutes, demonstrating the rapid hydrolysis of the acetate ester to the corresponding alcohol. Further metabolism of 2-ethylhexanol was demonstrated in the *in vivo* portion of the experiment, demonstrating the same downstream metabolites from 2-ethylhexyl acetate administration as has been reported from direct oral 2-ethylhexanol administration.

Metabolism data in humans for 2-ethylhexyl acetate are not available (OECD SIAM, 2010).

Hydrolysis rates of straight chain acetates were measured in respiratory (nasal) and liver tissues of rats, rabbits and Syrian hamsters by measuring the carboxylic acid formation (Dahl, 1987). The results indicated that esters are readily hydrolysed by respiratory tract enzymes. Species and tissue differences were apparent. The nasal ethmoturbinates of rabbit and hamster showed especially high levels of esterase activity, exceeding all other tissues tested, including the liver. For rats, the hydrolysis rates were highest in liver tissues and twice as high as in the nasal tissue (Table 1). Trachea activities were comparable to nasal activities while lung activities were much lower.

TABLE 1 HYDROLYSIS RATES[A] OF ESTERS BY RESPIRATORY TRACT AND LIVER TISSUE S-9 ENZYMES FROM RATS, RABBITS AND HAMSTERS (AFTER DAHL, 1987).

	Animal species substrate					
Tissues	**Rat**		**Rabbit**		**Hamster**	
	Pentyl acetate	Phenyl acetate	Pentyl acetate	Phenyl acetate	Pentyl acetate	Phenyl acetate
Maxilloturbinates	100 ± 8	230 ± 30	76 ± 13	560 ± 50	1110 ± 101	1700 ± 120
Ethmoturbinates	120 ± 5	250 ± 30	190 ± 2	740 ± 20	1300 ± 33	1700 ± 110
Trachea	110 ± 10	220 ± 6	80 ± 11	450 ± 40	930 ± 143	1300 ± 170

Lung	75 ± 4	110 ± 6	47 ± 2	390 ± 50	180 ± 4	520 ± 30
Liver	250 ± 6	510 ± 10	380 ± 14	610 ± 30	1100 ± 81	230 ± 30

[a] mean of 3-5 determinations. Units are nmol carboxylic acid formed/mg S-9 protein/min ± standard error

Among straight chain aliphatic alcohol acetates hydrolysis increased with carbon number up to pentyl alcohol. *n*-Butyl acetate, isobutyl acetate, and *sec*-butyl acetate may be readily hydrolysed to acetic acid and their respective alcohols in the blood, liver, small intestine, and respiratory tract, as has been shown in a number of *in vitro* experiments using homogenates from liver, small intestinal mucosa, and ethmoturbinates (Longland, 1977; Dahl, 1987). Branched 4-carbon alcohol acetates were less rapidly hydrolysed than n-butyl acetate (**Table 2**).

TABLE 2 EFFECT OF ALCOHOL CHAIN LENGTH AND HYDROPHOBICITY (EXPRESSED AS HYDROPHOBICITY CONSTANT AND OCTANOL-WATER PARTITION COEFFICIENT) ON HYDROLYSIS RATE OF ACETATES WITH RAT ETHMOTURBINATES S-9 (NASAL TISSUE).

Chemical	Hydrolysis rate ± standard error[a]	Hydrophobicity constant[d]	Log Kow
Methyl acetate	15 ± 3		0,18[b]
Ethyl acetate	30 ± 3		0,68[b]
Propyl acetate	56 ± 4		1,4[b]
n-Butyl acetate	77 ± 4	2,13	1,78 (Hansch et Leo, 1995)
iso-butyl acetate	67 ± 3	2,03	1,78 (Hansch et Leo, 1995)
sec-butyl acetate	62 ± 3	2,04	1,72 (Hansch et Leo, 1995)
tert-butyl acetate	42 ± 2	1,98	1,76 (Hansch et Leo, 1995)
Pentyl acetate	94 ± 4		2,3 (exp value in Kowwin)
Hexyl acetate	64 ± 4		3,3[b]
2-ethylhexyl acetate	38[c]		3,74 (HSDB, 2001)
Octyl acetate	47 ± 4		3,74 (HSDB 2001)

[a] Units are nmol carboxylic acid formed/mg S-9 protein/min (from Dahl (1987) except 2-ethylhexyl acetate)

[b] ECHA dissemination webpage (http://echa.europa.eu/information-on-chemicals) consulted on 22/3/2015

[c] own calculation

[d] Hansch and Leo, 1979

A bilinear model was derived for the correlation between hydrophobicity (expressed as hydrophobicity constant) and hydrolysis rate, for straight chain aliphatic esters (Dahl, 1987). Another parameter expressing hydrophobicity is the octanol-water partition coefficient (Kow). The higher the log Kow, the more lipophilic a substance is. Meteor, a commercially available tool that uses a knowledge-base of structure-metabolism rules to predict the metabolic fate of a query chemical structure, uses the log Kow to identify biotransformations that are not likely to occur, due to very low lipophilicity (ECHA, 2008). 2-Ethylhexyl acetate is a lipophilic substance (log Kow of 3,74) allowing biotransformation. However, log Kow is not the only parameter influencing the hydrolysis rate since the log Kow of pentyl acetate is lower, but the hydrolysis rate is higher than the calculated hydrolysis rate of 2-ethylhexyl acetate. This is in line with the findings of Meykenyan, who states that the log Kow is one of the factors influencing metabolism rate, besides water solubility and other physical-chemical properties (Meykenyan, 2004).

Steric hindrance at the hydrolysis site apparently contributes to the lower hydrolysis rate of branched acetate esters (Dahl, 1987). The difference in hydrolysis rate between n-butyl acetate and sec-butyl acetate is nearly 20% **(Table 2).** 2-Ethylhexyl acetate is a C8 molecule consisting of a C6 chain and a C2 branch. n-Octyl acetate is a C8 chain molecule. The hydrolysis rate of n-octyl acetate is 47 nmol carboxylic acid formed/mg S-9 protein/min for ethmoturbinates. The hydrolysis rate of 2-ethylhexyl acetate could be calculated as 80% of this value, being 38 nmol carboxylic acid formed/mg S-9 protein/min. Two factors that may neutralize one another are: on the one hand sec butyl acetate has the branch closer to the oxygen atom (reaction site of the esterase) than 2-ethylhexyl acetate so that the esterase may be less hindered by 2-ethylhexyl acetate compared to sec butyl acetate, on the other hand the branch is larger in 2-ethylhexyl acetate and hydrolysis may be slower.

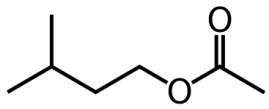
Dahl tested two nasal enzymes: maxilloturbinates and ethmoturbinates; the latter showed higher hydrolysis activity. Dahl calculated from experimental results that the nasal maxilloturbinates alone have 10 times the necessary capacity to completely hydrolyse phenyl acetate inhaled at 25ppm. The experimental difference between hydrolysis rate of phenyl acetate by maxilloturbinates and hydrolysis rate of octyl acetate by ethmoturbinates is about 5, so it can be assumed that the maxilloturbinates also have the necessary capacity (2 times) to completely hydrolyse octyl acetate (and 2-ethylhexyl acetate which has about the same (calculated) hydrolysis rate) inhaled at 25ppm. For rats hydrolysis activities in the liver are 2-3 times higher than with nasal maxilloturbinates (**Table 1**).

Experiments performed by Essig (1989) are in line with the findings of Dahl (1987) that *tert*-butyl acetate is less readily hydrolysed than n-butyl acetate. When added to blood samples

from male volunteers or female rats, respective hydrolysis half-lives of *n*-butyl acetate were 4 and 12 min, while those of *tert*-butyl acetate were 300 and 270 min (Essig, 1989). The difference in hydrolysis rate between n-butyl acetate and 2-ethylhexyl acetate is a factor 2 (**Table 2**), so the hydrolysis half-lives of 2-ethylhexyl acetate could be calculated to be less than 10 (2x4) and less than 30 minutes (2x12) in blood of man and rats respectively.

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food state that like with many other esters, it can be expected that 2-ethylhexyl acetate is rapidly hydrolysed in the GI tract to acetic acid and 2-ethylhexanol but that there is no experimental evidence for this (EFSA, 2008).

Aliphatic acyclic acids were evaluated for their safety as flavouring agents (JECFA, 1998). Hydrolysis is catalysed by classes of enzymes recognized as carboxylesterases or esterases. In mammals, these enzymes occur in most tissues throughout the body (Heymann, 1980; Anders, 1989) but predominate in the hepatocytes (Heymann, 1980). Select isoenzymes exhibit an increase in enzyme binding and maximum velocity as the carbon chain length of either the alcohol or carboxylic acid component of the substrate increases (Heymann, 1980 in JECFA, 1989). The hydrolysis of isopentyl acetate (3-methyllbutyl acetate) was measured *in vitro*.



In a test with pancreatin, 20% of the substance was hydrolysed after 2 hours. In whole homogenate of pig jejunum 100% was hydrolysed after 2 hours (JECFA, 1998).

B. Toxicokinetics of 2-ethylhexanol

Adsorption

The hydrolysis products acetic acid and 2-ethylhexanol of 2-ethylhexyl acetate are rapidly absorbed in the gastrointestinal tract (EFSA, 2008; IPCS, 1998).

In vitro percutaneous adsorption of 2-ethylhexanol was measured using full thickness rat skin and human stratum corneum (Barber, 1992). The absorption rates in rat and were 0,22±0,09 mg/cm²/hr for rat skin and 0,038±0,014 mg/cm²/hr for human skin. So the ratio rat/human was 5.78, indicating that the human skin is less permeable for the 2-ethylhexanol than the rat skin. The measured permeability constant (Kp) was $2{,}59 \cdot 10^{-4}$ cm/hr for rat skin and $4{,}54 \cdot 10^{-5}$ cm/hr for human skin.

The predicted Kp of 2-ethylhexanol is higher: 0.01525 cm/hr in COSMOS-SkinPermPred and 0,019 cm/hr in Dermwin v2.02.

Excretion

The metabolism of 2-ethylhexanol administered orally and dermally to female rats was studied by Deisinger (1994). Excretion balance was measured after single high (500 mg/kg) and low (50 mg/kg) oral doses, repeated low oral dosis (administration during 15 consecutive days), 6 hrs after dermal application of a 1 g/kg dose, and after 1 mg/kg intravenous application. In all scenario's [^{14}C] 2-ethylhexanol was used except during the first 14 days of the repeated dose study. The conclusions of the study were:

- The high, low and repeated low oral dose studies with 2-ethylhexanol showed similar excretion balance profiles of [^{14}C], with some evidence of metabolic saturation at the high dose.
- No evidence of metabolic induction was seen following the repeated low oral dosing
- All of the oral doses were eliminated rapidly, predominantly in the urine during the first 24h following dosing
- The dermal dosing resulted in only about 5% absorption of the 1 g/kg dose, with the major portion of the dose recovered unabsorbed from the dermal exposure cell at 6h
- Urinary metabolites eliminated following the oral and dermal doses were predominately glucuronides of oxidised metabolites of 2-ethylhexanol, including glucuronides of 2-ethyladipic acid, 2-ethylhexanoic acid, 5-hydroxy-2-ethylhexanoic acid and 6-hydroxy-2-ethylhexanoic acid

The major pathway for elimination of 2-ethylhexyl acetate metabolites is the urine in which large amounts of 2-ethylhexanoic acid and 2-ethyladipic acid can be found, mainly in the form of glucuronide conjugates. Conjugation with sulphate does not seem to occur. The other minor metabolites are usually found in the unconjugated form. 5-Hydroxy-2-ethylhexanoic acid may also be found in the form of a lactone, but it is not entirely clear whether this is a real metabolite or an artefact generated during sample clean-up. The available data further show that excretion of 2-ethylhexyl metabolites is virtually complete within 24-48 hours.

The excretion via glucuronides of the metabolites is confirmed in the HSDB database which mentions that as with other acetate esters, 2-ethylhexyl acetate is likely metabolised to the alcohol (2-ethylhexyl alcohol) and 90% of an administered dose (to rabbits) is excreted as the glucuronides (HSDB, 1995) .

According to experts of the International Programme on Chemical Safety, aliphatic acyclic primary alcohols are oxidized to their corresponding carboxylic acids, which are either conjugated and excreted in the urine, or undergo ß-oxidation and cleavage (IPCS, 40).

Another metabolite of 2-ethylhexyl acetate is acetate. When acetate is administered to animals, only a small amount can be recovered from the urine (Smyth, 1946).

Metabolism

The hydrolysis of 2-ethylhexyl acetate to 2-ethylhexanol is rapid. The subsequent metabolism of 2-ethylhexanol to 2-ethylhexaldehyde is presumed to occur with subsequent oxidation of the aldehyde intermediate to 2-ethylhexanoic acid. Metabolism and toxicokinetics studies with 2-ethylhexanol have demonstrated the presence of 2-ethylhexanoic acid in the plasma as well as glucuronide conjugates and oxidation products of 2-ethylhexanoic acid metabolism in the urine following intravenous, dermal and oral exposures. Elimination of 2-ethylhexanol metabolites following oral exposure was complete within 24 hours. Comparison of 2-ethylhexanol and 2-ethylhexanoic acid metabolic/toxicokinetics information and toxicity databases suggests that the metabolic processes necessary to convert 2-ethylhexanol to 2-ethylhexanoic acid explain the difference in toxicity of these chemicals (SIAM, 2010).

In its report for EFSA, experts concluded that 2-ethylhexanoic acid, 2-ethylhexanal and 2-ethylhexanol are rapidly absorbed from the gastrointestinal tract (EFSA, 2008). With respect to the 2-ethylhexyl moiety, it has been demonstrated in vitro that 2-ethylhexanol is converted into 2-ethylhexanal. The oxidation of 2-ethylhexanal to 2-ethylhexanoic acid has not specifically been studied, but based on the observation that *in vivo* 2-ethylhexanoic acid and metabolites thereof are major metabolites of 2-ethylhexanol, it can be assumed that *in vivo* 2-ethylhexanal is oxidised to give 2-ethylhexanoic acid. 2-Ethylhexanoic acid in turn is resistant to the normal fatty acid beta-oxidation pathway. Although some beta-oxidation may occur, the ultimate degradation of the molecule is blocked by the 2-ethyl side chain. After the first step in this beta-oxidation, carbon dioxide may be released (i.e. the C_1carbon atom), ultimately resulting in the formation of 2- or 4-heptanone. However, in rodents this seems to be a minor pathway, which may cover approximately 7 % of the dose. More important is omega and omega-1 oxidation, leading to the formation of 2-ethyladipic acid, 6-hydroxy-2-ethylhexanoic acid, 5-hydroxy-2-ethylhexanoic acid and several further oxidised products such as 2-ethyl-delta5-hexenoic acid (EFSA, 2008). No quantification or time is given.

Another metabolite is acetic acid. Acetate is readily metabolized. Living organisms use acetate to generate energy through oxidation into carbon dioxide and chemical energy in the form of adenosine triphosphate (ATP), in the so-called citric acid cycle.

Already in 1946 Smyth showed that acetate is rapidly metabolised. Cats were intravenously injected with 2M solutions of sodium acetate. The injected acetate very rapidly disappeared from the blood stream. The rapid disappearance might be due to excretion of acetate in the urine, diffusion of acetate into the extracellular and intracellular fluids (seen during the first

30 minutes after injection), or consumption of acetate by the tissues. Only a very small part (3, 4, 6, 14 and 18%) is excreted through the urine. By comparing acetate disappearance in intact animals and animals in which the liver was removed from circulation, the liver was seen to be responsible for about half the acetate metabolism. The influence of the liver on the disappearance of acetate from the blood stream was studied after injection of acetate in intact animals and in nephrectomised and eviscerated animals. It was experimentally shown by the authors that removing the kidneys had little influence on the acetate disappearance. The fall in acetate concentration was 1.72 (intact animals) and 0.85 mmol/100 ml/hr showing that the liver seems to be responsible for about the half the acetate metabolism in the cats.

C. Read across from 2-ethylhexanol

The use of 2-ethylhexanol studies for the evaluation of potential systemic toxicity of 2-ethylhexyl acetate is overall accepted and applied in the reports of scientific advisory groups.

The European Commission's Joint Research Centre (DG JRC) has published a report on the health based evaluation of indoor emissions from construction products (JRC, 2013). This report describes a harmonised procedure for establishing a list of compounds and their associated LCI (Lowest Concentration of Interest) values for the evaluation of emissions from construction products. For the determination of the LCI of 2-ethylhexyl acetate the report states that read across from 2-ethylhexanol has to be applied, thereby taking into account the difference in molecular weight between 2-ethylhexyl acetate and 2-ethylhexanol.

The Task Force of the OECD-SIAM (2010) considers that the toxicity information of 2-ethylhexanol is an appropriate surrogate for identifying hazards associated with systemic exposures to 2-ethylhexyl acetate since

1) 2-ethylhexyl acetate is rapidly and completely hydrolysed to 2-ethylhexanol within mammalian organisms, and
2) the limited toxicity information for 2-ethylhexyl acetate suggests a similar toxicity profile with 2-ethylhexanol.

The experts used read-across from 2-ethylhexanol for the evaluation of the systemic toxicity of 2-ethylhexyl acetate.

Also EFSA and IPCS accept that 2-ethylhexyl acetate is rapidly hydrolysed and that its hydrolysis products acetic acid and 2-ethylhexanol are rapidly absorbed by the GI tract where they may exert toxicity.

CONCLUSIONS

Acetate esters of primary alcohols undergo rapid hydrolysis, catalysed by esterases and proteases found in mammalian tissues and gastric fluids. The rapid and complete hydrolysis of 2-ethylhexyl acetate to 2-ethylhexanol has been demonstrated to occur *in vitro* within rat blood (half-life of 2.3 minutes) and *in vivo*. Further metabolism of 2-ethylhexanol (derived from orally administered 2-ethylhexyl acetate) to 2-ethylhexanoic acid was demonstrated in the *in vivo* portion of the experiment, demonstrating the same metabolites from 2-ethylhexyl acetate administration as has been reported from direct 2-ethylhexanol administration. The hydrolysis reaction occurs in the gut, respiratory tissue, and skin thereby allowing the corresponding alcohol to be absorbed into the systemic circulation.

In vitro test results with other simple carboxylic esters also seem to indicate a rapid hydrolysis to the corresponding alcohol and carboxylic acid. Branching may slightly slow down the hydrolysis reaction.

Based on the indications for rapid hydrolysis of acetate esters of primary alcohols, supported by short-time measured hydrolysis rates *in vitro*, read-across from 2-ethylhexanol to 2-ethylhexyl acetate can be accepted for the evaluation of systemic effects from exposure to 2-ethylhexyl acetate. The test results with the alcohol can be used for the evaluation of systemic toxicity of the acetate. Acetic acid is also a metabolite but this substance is of no health concern.

Read-across from 2-ethylhexanol to 2-ethylhexyl acetate cannot be accepted for the evaluation of local effects, such as skin and eye irritation.

ADVICE

No need to request further information concerning the approach of read across from 2-ethylhexanol for toxicity endpoints dependent upon systemic exposure.

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MEMBERS OF THE SCIENTIFIC COMMITTEE

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CONFLICT OF INTEREST

No member has declared any conflict of interest.

RAPPORTEUR

The Scientific Committee REACH thanks the rapporteur Lieve Geerts.

ADOPTION OF THE ADVICE

The Scientific Committee REACH advice was adopted by consensus at the meeting of 7/5/2015.

LEGAL FRAMEWORK OF THE ADVICE

Cooperation agreement of 17 October 2011 between the Federal State, the Flemish Region, the Walloon Region and the Brussels Capital Region concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

Ministerial decree appointing the members of the Scientific Committee REACH established under Article 3, § 3 of the Cooperation Agreement of 17 October 2011 between the Federal State, the Flemish Region, the Walloon Region and the Brussels Capital Region concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

DISCLAIMER

The Scientific Committee REACH reserves, at any time, the right to change this advice when new information and data become available after the publication of this version.

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c /o

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