UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
Bethesda, MD 20814

Memorandum

Date: October 24, 2010

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SUBJECT : Toxicity Review of **Di-C9-11-alkyl phthalate (D911P)**

The following memo provides the Versar, Inc. and SRC, Inc. contractor's and U.S. Consumer Product Safety Commission's (CPSC's) Health Sciences staff assessment of the potential toxicity associated with **D911P**.

CPSC staff assesses a product's potential health effects to consumers under the Federal Hazardous Substances Act (FHSA). The FHSA is risk-based. To be considered a "hazardous substance" under the FHSA, a consumer product must satisfy a two-part definition. First, it must be "toxic" under the FHSA, or present one of the other hazards enumerated in the statute. Second, it must have the potential to cause "substantial illness or injury during or as a result of reasonably foreseeable handling or use." Therefore, exposure and risk must be considered in addition to toxicity when assessing potential hazards under the FHSA (CPSC, 1992; summarized at 16 CFR 1500.135)

The FHSA addresses both acute and chronic hazards. While the FHSA does not require manufacturers to perform any specific battery of toxicological tests to assess the potential risk of chronic health hazards, the manufacturer is required to label a product appropriately according to the requirements of the FHSA. The first step in the risk assessment process is hazard

* This report was prepared for the Commission pursuant to contract CPSC-D-06-0006. It has not been reviewed or approved by, and may not necessarily reflect the views of, the Commission.

identification, that is, a review of the available toxicity data for the chemical under consideration and a determination of whether the chemical is considered “toxic”. Chronic toxicity data (including carcinogenicity, neurotoxicity, and reproductive and developmental toxicity) are assessed by the CPSC staff using guidelines issued by the Commission (CPSC, 1992). If it is concluded that a substance is “toxic” due to chronic toxicity, then a quantitative assessment of exposure and risk is performed to evaluate whether the chemical may be considered a “hazardous substance”. This memo represents the first step in the risk assessment process; that is, the hazard identification step.

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FINAL

TOXICITY REVIEW FOR DI-(C9-C11 ALKYL) PHTHALATE (D911P)

Contract No. CPSC-D-06-0006
Task Order 012

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LIST OF ABBREVIATIONS AND ACRONYMS

D911P	Di-(C9-C11 alkyl) phthalate
GD	Gestation day
LOAEL	Lowest-observed-adverse-effect level
LD_{50}	Median lethal dose
NOAEL	No-observed-adverse-effect level
PND	Postnatal day
TWA	Time-weighted average

EXECUTIVE SUMMARY

D911P is a high production volume plasticizer found in a variety of consumer products.

Exposure to D911P resulted in oral LD_{50}s >6200 mg/kg in two animal studies. In addition, slight dermal irritation was noted in one well-described guinea pig study, while two rabbit studies did not report any irritation or corrosion. Sensitization was not reported in one well described animal study. Insufficient data were available to make the determination of whether D911P was associated with acute dermal or inhalation toxicity, eye irritation, or eye corrosion.

Evidence supported the conclusion that D911P was a subchronic toxicant. Exposure to D911P induced decrements in F0 and F1 body weight, food consumption, distribution of days in gestation and minor effects on number of live litters, implantation sites, litter size, and mean pup weights at later postnatal days, and the age of preputial separation. Epididymal, liver, seminal vesicle, and testes relative organ weights were also significantly increased in the F0 generation and relative testes weights in the F1 generation. Uterine + cervix relative weights were significantly decreased in the F0 generation and marginally affected in the F1 generation. Exposure to D911P resulted in gross or histopathologic changes to the liver, the epididymides, and the testes. Exposures also resulted in the development of minor skeletal variants in pups, such as a 14^{th} supernumerary rib and dilated renal pelves.

Acceptable daily intakes values (ADI's) are calculated when a given chemical is considered "toxic" and sufficient toxicity information is available. The ADI is the amount of a chemical that one may be exposed to on a daily basis without posing a significant risk of health effects to consumers. ADI's were not estimated for D911P relevant exposure durations for the general population or for other sensitive subpopulations because confirmatory data on toxicological endpoints were not available.

Even though NOAELs and LOAELs could be described for a particular study, the lack of supporting studies for certain toxicological endpoint suggests that there was "inadequate evidence" for the designation of D911P as a "chronic hazard" when considering FHSA criteria (16 CFR §1500.135).

TOXICITY REVIEW FOR DI-(C9-C11 ALKYL) PHTHALATE (D911P, CASRN 68515-43-5)

1. INTRODUCTION

This report provides the available data for the identity, physicochemical properties, manufacture and use, toxicity, and exposure information on di-(C9-C11 alkyl) phthalate (D911P). Historically, concerns over the use of phthalates have been associated particularly with the potential for reproductive/developmental effects from a human health view point (NICNAS, 2008). In addition, concerns that the structural and physicochemical properties of certain phthalates used as plasticizers may permit migration and leaching resulting in potential human exposure, particularly in soft plastics (NICNAS, 2008). Combining the potential for exposure and a recognized toxicity profile for some particular phthalates has raised concerns over potential health risks, especially when used in consumer products (NICNAS, 2008).

2. IDENTITY and PHYSICOCHEMICAL CHARACTERISTICS

This section highlights the identity and key physicochemical properties of D911P. D911P is considered to belong to the High Molecular Weight Phthalate Esters (HMWPE) group by the OECD (NICNAS, 2008). It consists of esters with alkyl carbon backbone of ≥ C7. Structurally, D911P has linear and branched alkyl esters. The identity and physicochemical properties of D911P can be seen in Tables 2.1 and 2.2 (NICNAS, 2008; U.S. EPA, 2010).

Table 2.1 Names, Structural Descriptors, and Molecular Formulas of D911P (NICNAS, 2008)

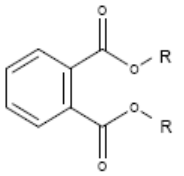
CAS Number:	68515-43-5
Chemical Name:	1,2-Benzenedicarboxylic acid, di-C9-11 branched and linear alkyl esters
Common Name:	Di-C9-11-alkyl phthalate (Di-C9-11 PE)
Molecular Formula:	C28H46O4
Structural Formula:	 R= C9H19 to C11H23 (branched and linear) [>80% linear]
Molecular Weight:	446.7 (based on a di-C10 phthalate ester)
Synonyms:	Di-C9-11 branched and linear alkyl ester
Purity/Impurities/Additives:	Purity: >99.5% w/w; Impurity 0.1-0.2% w/w anti oxidant; Additives: none

Table 2.2 Physicochemical Properties of D911P	
Property	**Value**
Physical state	colorless oily liquid (NICNAS, 2008)
Melting point	-45°C - -9°C (NICNAS, 2008; U.S.EPA, 2010)
Boiling point	454°C - 501°C (101.3 kPa) (NICNAS, 2008)
Density	960 kg/m3 (20°C) (NICNAS, 2008)
Vapor pressure	(4.97 - 68.10) x 10^{-10} kPa (25°C) (NICNAS, 2008); 2.0 x 10^{-7} (U.S.EPA, 2010)
Water solubility	<0.1 g/L (20°C) (NICNAS, 2008)
Partition coefficient n-octanol/water (log Kow)	8.6 - 10.3 (NICNAS, 2008; (U.S.EPA, 2010))
Henry's law constant	3.4 x 10^{-5} (U.S.EPA, 2010)
Flash point	223ºC (ChemSpider, 2011)

3. MANUFACTURE, SUPPLY, AND USE

Manufacture

In general, D911P is manufactured commercially in a closed system by catalytically esterifying phthalic anhydride with linear C9-11 alcohols (dinonyl, didecyl, diundecyl). As with other phthalates, the unreacted alcohols are recovered and reused, and the D911P mixture is purified by vacuum distillation or activated charcoal. The purity of D911P can achieve 99% or greater using current manufacturing processes. Certain D911P mixtures have been manufactured under the name Bisoflex L911P using linear Linevol 911 alcohols with >97% carbon distributions in the C9-C11 range. The relative distribution of carbon chains in this mixture is typically 13-23% C9, 37-47% C10, and 33-43% C11 (ECB, 2000). The remaining fraction of the D911P commercial mixture may contain 0.1-0.2 wt% of anti-oxidants (NICNAS, 2008) and a maximum of 0.1% water (ExxonMobil, 2001).

Supply

U.S. production and consumption estimates for specifically D911P or associated products were limited in detail in the reports reviewed (Bizarri et al., 2007, 2009). Supply data on linear C7-C9, linear C7-C11, and linear C9-C11 phthalates have been used to supplement information on D911P.

Recently, U.S. production of linear C9-C11 phthalates was reported as 30,000 metric tons (2008) and projected to decline to 22,000 metric tons (2013). Linear C9-C11 phthalate's

proportion of the total phthalate production market (5.1%) is also projected to decline (to 3.9%) during the same period (-6.0% growth rate; Bizzari et al. 2009).

U.S. consumption of linear C9-C11 phthalates was reported as 29,000 metric tons (2008) and projected to decline to 21,000 metric tons (2013). Linear C9-C11 phthalate's proportion of the total phthalate consumption market (4.8%) is also projected to decline (to 3.6%) during the same period (-6.3% growth rate; Bizzari et al. 2009).

In 2008, U.S. consumption of linear C9-C11 phthalates has been within a metric ton or two less than production estimates, and currently, percentages of total phthalate consumption market are similar to production. This suggests that most linear C9-C11 phthalates produced in the U.S. are utilized locally and that small amounts may be exported.

In general, the production of linear C7-C11 phthalates slowly increased from 1982 to 1999 (91,000 to 118,000 metric tons) and then gradually declined to 107,000 metric tons in 2005 (Bizzari, 2007, 2009).

U.S. consumption estimates of linear C7-C11 phthalates for the period between 1983 and 1993 were on average 9,000 metric tons less than production estimates. From 1995 to 1997, consumption exceeded production by an average of 6,000 metric tons. From 2000 until 2005, U.S. consumption of linear C7-C11 phthalates has roughly matched production.

Currently, ExxonMobil Chemical is the major U.S. producer of linear C7-C11 phthalates. Sterling Chemicals, Inc. (BASF) is the second largest U.S. producer.

U.S. EPA (2010) reported that the production and/or import volume range for D911P was 10 million to <50 million pounds in 2005. These production volumes reflect non-confidential information for chemicals reported under the U.S. EPA Inventory Update Rule**.**

Use

D911P plasticizers reportedly have low volatility, good cold flexibility, and resistance to photodegradation.

The non-confidential industrial processing and uses reported in the 2006 Inventory Update Rule submission included chemical product and preparation manufacturing, plastic

manufacturing and basic organic chemical manufacturing (U.S. EPA, 2010). The non-confidential consumer and commercial uses included electrical and electronic products, textiles and apparel, rubber and plastic products, and fabrics (U.S. EPA, 2010). Godwin (2010) reported examples of plasticizers used in different market segments. General uses reported for linear C9-11 in the following segments are: automotive (exterior paint and wiring; interior and exterior trim); construction (vinyl siding, roofing and urethane sealants, steel cladding); household (furniture); wire and cable (building wire and wire and cable-other). D911P has also been reported to be used as a lining for cargo or ballast tanks in marine operations. Diplast® L9-11 has reported uses in PVC roofing, anti-fog synthetic leather car interiors, auto electric cables, and advertisement graphics (POLYNT S.p.A., 2011). Jayflex911P (ExxonMobil Chemical, 2001) and Palatinol 911P (BASF, 2009) have listed applications that include wire and cable insulation for autos and communication, low temperature, high performance film and sheeting, and low fog auto interiors.

4. TOXICOKINETICS

No toxicokinetic data were located for D911P.

5. HAZARD INFORMATION

This section contains brief hazard summaries of the adverse effects of D911P in a variety of animal and bacterial species. More detailed discussions of the studies can be viewed in the Appendices. When evaluating hazard study data, Consumer Product Safety Commission (CPSC) staff utilized the definitions for toxicity as presented in regulations (16 CFR §1500.3(c)(2)(ii)) and the chronic hazard guidelines (16 CFR §1500.135) in the Federal Hazardous Substances Act (FHSA; 15 U.S.C. 1261-1278). When considering the FHSA, substances that are "known" or "probable" toxicants are "toxic" and substances that are considered "possible" toxicants are "not toxic" (Table 5.1).

Table 5.1. Classification of Chronic Hazards (as per the FHSA)

Evidence	Human Studies	Animal Studies
Sufficient evidence	**Known***	**Probable**
Limited evidence	**Probable**	Possible
Inadequate evidence	Possible	—
*Classifications in bold are considered *toxic* under FHSA		

Exposure to D911P resulted in oral LD_{50}s >6200 in two animal studies. In addition, slight dermal irritation was noted in one well-described guinea pig study, while two rabbit studies did not report any irritation or corrosion. Sensitization was not reported in one well described animal study. Insufficient data were available to make the determination of whether D911P was associated with acute dermal or inhalation toxicity, eye irritation, or eye corrosion.

Evidence supported the conclusion that D911P was a subchronic toxicant. Exposure to D911P induced decrements in F0 and F1 body weight and food consumption, changes in the distribution of gestation length, minor effects on number of live litters, implantation sites, litter size, and mean pup weights at later postnatal days, and a difference in the age of preputial separation. Epididymal, liver, seminal vesicle, and testes relative organ weights were also significantly increased in the F0 generation and relative testes weights in the F1 generation. Combined uterine cervical relative weight was significantly decreased in the F0 generation and marginally, albeit insignificantly, in the F1 generation. Exposure to D911P also resulted in gross and/or histopathologic changes to the liver, the epididymides, and the testes. Exposures also resulted in the development of minor skeletal variants in pups, such as a 14^{th} supernumerary rib and dilated renal pelves.

Acceptable daily intakes values (ADI's) are calculated when a given chemical is considered "toxic" and sufficient toxicity information is available. The ADI is the amount of a chemical that one may be exposed to on a daily basis without posing a significant risk of health effects to consumers. ADI's were not estimated for D911P relevant exposure durations for the general population or for other sensitive subpopulations because confirmatory data on toxicological endpoints were not available.

In the following discussions, hazard information was divided into sections thought to be of interest for regulatory matters (i.e., for labeling and other mitigation measures) as well as for biological and pathological consistency. More specifically, hazards were divided into whether the exposure was singular or repeated. Hazards associated with repeated exposures were further divided into groupings based on the affected organ system (i.e., hepatic, neurological, hematologic, etc.) and discussed in terms of the exposure duration if sufficient information existed to do so (***acute***, ≤14 days; ***intermediate-term*** or ***subchronic***, 15–364 days; ***long-term*** or ***chronic***, ≥365 days; and ***multigenerational***; ATSDR, 2007) where appropriate. Discrete study information can be reviewed in the Appendices.

ACUTE DOSE TOXICITY

5.1. Acute Oral Toxicity

No deaths occurred in a single-dose toxicity study of male and female CFE rats and CF1 mice (4/sex/species/dose level) administered undiluted D911P via gavage at up to 19,700 mg/kg and observed for 10 days following dosing (Brown et al., 1970). Persistent wet fur was observed in treated rats and mice (restricted to the perianal area in mice). The only other acute oral toxicity information located was an LD_{50} >6,200 mg/kg for D911P in rats in an unpublished study (BASF AG, 1971, as reported in NICNAS, 2008). The same study reported an LD_{50} >6,200 mg/kg for D911P administered to mice via intraperitoneal injection (BASF AG, 1971, as reported in NICNAS, 2008).

Sufficient methodological details were provided in these studies to consider them acceptable for use. The estimated LD_{50} values from Brown et al. (1970) and unpublished BASF AG (1971) studies were substantially higher than the oral LD_{50} range (50–5,000 mg/kg) established by the FHSA as "acutely toxic" (16 CFR §1500.3(c)(2)(i)(A)).

5.2. Acute Dermal Toxicity

No information was located regarding the acute dermal toxicity of D911P.

The lack of acute dermal toxicity data for D911P can be considered a data gap and supports the conclusion that there is "inadequate evidence" for the designation of D911P as "acutely toxic" via dermal exposure under the FHSA (16 CFR §1500.3(c)(2)(i)(C)).

5.3. Acute Inhalation Toxicity

No mortality was observed in rats exposed for 8 hours to a saturated atmosphere of D911P vapors generated at 20°C; an unspecified number of mortalities occurred in other rats during a 1-hour exposure to D911P vapors generated at 180°C (unpublished report of BASF AG, 1971 [as reported in European Commission, 2000]). Additional study details were not available in the European Commission (2000) summary.

The lack of methodological and acute inhalation toxicity data for D911P can be considered a data gap and supports the conclusion that there is "inadequate evidence" for the designation of D911P as "acutely toxic" via inhalation under the FHSA (16 CFR §1500.3(c)(2)(i)(B)).

5.4. Primary Skin Irritation

Brown et al. (1970) found no gross or histopathological evidence of dermal irritation in New Zealand white rabbits exposed to D911P in covered and uncovered tests. In the covered test, four rabbits of each sex had D911P (1 mL undiluted; 20% C9, 45% C10, 35% C11 by weight) applied to the dorsal skin (clipped, but not abraded) on 3 consecutive days under occluded conditions and immobilized for 6 hours following each application. The skin was scored for erythema and edema visually for 7 days after the first application, after which the skin was collected and processed for histopathological examination. In the uncovered test, one rabbit of each sex was given a dermal application of D911P (1.0 mL undiluted) to dorsal skin (clipped weekly) 5 days/week for 3 weeks. Visual assessment of the skin was performed daily, and followed by collection of skin for histopathological examination the day after the final application. No evidence of dermal irritation was observed in test rabbits under conditions described here. D911P was also found to be nonirritating to rabbit skin in an unpublished study by BASF AG (1971, as cited in NICNAS, 2008). Brown et al. (1970) performed an uncovered

irritation test in guinea pigs using similar procedures to their uncovered rabbit test, but using a dose of 0.5 mL/day and including five animals of each sex. Coarse, slightly thickened skin and some sloughing of the surface layers at the application site were noted in the guinea pigs.

In summary, slight dermal irritation was noted in one well-described guinea pig study while two rabbit studies did not report any irritation. The estimated "scores" from the guinea pig and rabbit studies are not expected to exceed 5.0, the threshold for defining a skin irritant under the FHSA (16 CFR §1500.3(c)(4)). A weight of evidence also supports the conclusion that D911P does not fit the definition of "corrosive" (16 CFR §1500.3(c)(3)) when considering FHSA criteria.

5.5. Primary Eye Irritation

D911P was reported to be nonirritating to the rabbit eye (Brown et al., 1970; BASF AG, 1971, as cited in NICNAS, 2008). Additional study details were not available.

The lack of additional information on the ocular properties of D911P can be considered a data gap and supports the conclusion that there is "inadequate evidence" for the designation of D911P as a "primary ocular irritant" or "corrosive" under the FHSA (16 CFR §1500.3(c)(3) and 16 CFR §1500.3(c)(4)), respectively.

5.6. Sensitization

D911P did not induce a sensitization response in male (n=5) or female (n=5) guinea pigs receiving the test substance by subcutaneous injection (0.1% in paraffin) or by application to the dorsal skin 3 days/week for 3 weeks, followed by a 10-day rest period and challenge with the same solution (Brown et al., 1970). Sensitization reactions were assessed at 1, 24, and 48 hours following challenge.

D911P did not induce sensitization in guinea pigs following exposure via two routes of administration, supporting the conclusion that D911P does not fit the definition of a "strong sensitizer" as defined in the FHSA (16 CFR §1500.3(c)(5)).

REPEAT DOSE TOXICITY

5.7. General Effects (Clinical Signs, Food/Water Consumption, Body Weight)

In a two-generation reproductive toxicity study (Willoughby et al., 2000) in which male and female Sprague-Dawley rats were administered diets containing D911P (Bisoflex L911P; 13-23% C9, 37-47% C10, 33-43% C11) at 0.1, 0.5, or 1.0% for two generations, mean body weights of high-dose F0 males (approximate dose of 1,510 mg/kg-day; see Appendix B, Table B.1 for explanation of dose estimates) were up to 25% lower (in a dose-related fashion) than controls during a 10-week pre-mating period. The depressed body weight was accompanied by reduced food intake (also dose-related). Food intake was significantly lower than controls after premating treatment week 2 and was approximately 85% that of controls by the end of treatment week 10. At terminal sacrifice, after approximately 18 weeks of D911P exposure (10 weeks pre-mating and during mating, gestation, and 2 weeks following delivery), mean body weight of the high-dose F0 males was 19% lower than controls (Table 5.2). Mean body weight in high-dose F1 parental male rats (approximate dose of 1,238 mg/kg-day) was also significantly lower than that of controls, beginning at the end of treatment week 5, and as much as 12% lower than controls at terminal sacrifice (Table 5.2). The high-dose F1 parental males consumed slightly less food than controls, but the difference was not statistically significant. There were no effects on body weight or food consumption in F0 or F1 parental male rats treated with lower doses of D911P.

Table 5.2. Results of Body Weight Assessments in Sprague-Dawley Rats Exposed to D911P in the Diet for Two Generations

Dietary D911P concentration (percent)	**0**	**0.1**	**0.5**	**2.0/1.0[a]**	**0**	**0.1**	**0.5**	**1.0**
Parental males	**F0**				**F1**			
Number of animals	27	28	28	28	28	28	28	27
Terminal body weight (g)	639 ± 71[b]	653 ± 70	625 ± 71	517 ± 69[c]	611 ± 72	621 ± 86	634 ± 82	538 ± 64[c]
Parental females	**F0**				**F1**			
Number of animals	24	23	22	23	26	23	23	24
Terminal body weight (g)	351 ± 28[b]	356 ± 27	342 ± 20	337 ± 24	341 ± 31	343 ± 34	333 ± 23	325 ± 24[d]

[a]The D911P concentration in the food of F0 rats was 2.0% during the first 6 treatment weeks; reduced to 1.0% in the high-dose groups for remainder of study.
[b]Mean ± standard deviation.
[c]Significantly different from controls ($p < 0.01$) by Behrens-Fisher or Dunnett's test.
[d]Significantly different from controls ($p < 0.05$) by Behrens-Fisher or Dunnett's test.

Source: Willoughby et al. (2000).

In the same study, high-dose F0 females (approximate dose of 1,389 mg/kg-day) exhibited slightly, but statistically significant dose-related, lower mean body weights than controls for the last half of the premating period and at some (but not all) time points during gestation and lactation. Mean body weights of D911P-treated F0 female rats at terminal sacrifice were not significantly different from controls (Table 5.2). There were no significant body weight effects in F1 parental females during the premating period, but mid- and high-dose F1 parental females (approximate doses of 623 and 1,264 mg/kg-day, respectively) exhibited slightly ($p < 0.05$) lower mean body weights than controls at some (but not all) time points during gestation and lactation. The mean terminal body weight of the high-dose F1 parental females was 5% lower than that of controls ($p < 0.05$); there were no difference from controls at lower doses (Table 5.2). Body weight was also reduced in a dose-related fashion in dams during gestation and lactation (data not shown).

Although some statistically significant differences from controls were found for parental female body weights in this study, the changes were small (within 10% of controls at all times) and somewhat sporadic in occurrence. Food consumption was similar for all female treatment groups of both parental generations throughout the study. No clinical signs of toxicity were reported in parental males or females in this study.

In a developmental toxicity study (Fulcher et al., 2001) of female Sprague-Dawley rats administered D911P (Bisoflex L911P; 13-23% C9, 37-47% C10, 33-43% C11) by gavage daily on gestation days (GDs) 1–19 at doses of 250, 500, or 1,000 mg/kg-day, no effects on maternal body weight or food consumption were found. Increased salivation was observed sporadically in all dams after dosing, particularly high-dose dams, and was considered by the researchers to reflect distaste for the dosing formulation. Staining of the fur and hair loss were noted in all dose groups, including controls, and were thought to have been related to the use of olive oil vehicle.

A clinical sign described only as “general depression” was noted in CFE rats (8/sex) administered undiluted D911P by gavage at 4,800 mg/kg-day for 7 consecutive days; no other clinical signs of toxicity were reported (Brown et al., 1970).

5.8. Hepatotoxicity

In two generations of Sprague-Dawley rats exposed to 0.1, 0.5, or 1% D911P in the diet (Willoughby et al., 2000), high-dose F0 and F1 parental male rats (approximate doses of 1,510

and 1,238 mg/kg-day, respectively) exhibited significantly decreased mean absolute liver weights (Table 5.3). The decreases in absolute liver weight correlate roughly with the observed decreases in body weight in these same groups. Relative liver weights were not reported, but when calculated, increased in a dose-related fashion in F0, but not F1 rats. Lesions of the periacinar hepatocytes (fatty vacuolation, hypertrophy, necrosis) were significantly increased in a dose-related fashion in mid- and high-dose F0 and F1 parental male rats (Table 5.3). Additional lesions found at increased incidences in the high-dose males were regenerative hyperplasia, bile duct proliferation, and clear cell, basophilic, and eosinophilic foci. Evaluations of livers from mid- and high-dose F1 males revealed significantly increased palmitoyl CoA oxidase activity, suggestive of a treatment-related peroxisomal proliferative effect; the high-dose group exhibited nearly 2-fold higher palmitoyl CoA oxidase activity than that of controls.

Absolute and relative liver weights were also increased in a dose-related fashion in male and female pups sacrificed at PND 25. Significant increases ($p < 0.01$ or 0.05) were reported for absolute liver weights from high-dose F1 males and female pups, and mid- and high-dose males and female pups in the F2 generation, although the study authors noted the absence of apparent treatment-related morphological liver changes in the pups.

Table 5.3. Liver Evaluation Data for Sprague-Dawley Rats Receiving D911P from Diet for Two Generations								
Dietary D911P concentration (percent)	**0**	**0.1**	**0.5**	**2.0/1.0[a]**	**0**	**0.1**	**0.5**	**1.0**
Parental males	**F0**				**F1**			
Number of animals assessed for liver weight	27	28	27	28	28	28	28	26
Absolute liver weight (g)	24.2 ± 4.5[b]	24.7 ± 3.5	24.3 ± 4.0	20.7 ± 6.0[c]	23.5 ± 4.2	24.1 ± 4.4	25.9 ± 6.9	19.9 ± 3.4[d]
Relative liver weight (%)	3.81	3.78	3.89	4.00	3.85	3.88	4.09	3.70
Incidences of histopathologic liver lesions:								
Regenerative hyperplasia	0/28	0/7	0/11	7/28[e]	0/28	0/3	0/12	18/28[f]
Bile duct proliferation	0/28	0/7	1/11	24/28[f]	1/28	0/3	1/12	23/28[f]
Clear cell foci	0/28	0/7	1/11	24/28[f]	0/28	0/3	0/12	13/28[f]
Basophilic foci	0/28	0/7	1/11	22/28[f]	0/28	0/3	0/12	16/28[f]
Eosinophilic foci	0/28	0/7	0/11	8/28[g]	0/28	0/3	0/12	3/28
Periacinar hepatocytes:								
Fatty vacuolation	0/28	0/7	9/11[h]	23/28[f]	2/28	0/3	8/12[h]	18/28[f]
Hypertrophy	0/28	1/7	5/11[h]	20/28[f]	0/28	0/3	5/12[h]	24/28[f]
Necrosis	0/28	0/7	3/11[h]	28/28[f]	0/28	0/3	3/12[h]	25/28[f]
Pigment	0/28	0/7	0/11	1/28	0/28	0/3	0/12	10/28[f]
Parental females	**F0**				**F1**			
Number of animals assessed for liver weight	24	23	22	23	26	23	23	24
Absolute liver weight (g)	19.9 ± 2.5[b]	20.9 ± 2.6	24.3 ± 1.8[d]	25.1 ± 2.1[d]	20.5 ± 2.7	20.9 ± 2.7	23.4 ± 2.6[d]	25.2 ± 2.6[d]
Relative liver weight (%)	5.67	5.87	7.11	7.45	6.01	6.09	7.03	7.75
Incidences of histopathologic liver lesions								
Periacinar hepatocytic fatty vacuolation	0/28	0/2	1/5	8/28[g]	0/28	0/2	3/11	4/28
Periacinar hepatocytic hypertrophy	0/28	0/2	0/5	7/28[e]	0/28	0/2	2/11	2/28
Offspring sacrificed at postnatal day 25	**F1**				**F2**			
Absolute liver weight (g) Males	4.27 ± 0.80[b]	4.23 ± 0.53	4.64 ± 0.74	4.95 ± 0.82[c]	4.36 ± 0.55	4.47 ± 0.48	4.88 ± 0.83[d]	4.69 ± 0.54[d]
Relative liver weight (%) Males	6.08	5.99	6.65	7.30	5.95	6.23	6.96	7.28
Absolute liver weight (g) Females	3.95 ± 0.75	3.90 ± 0.59	4.32 ± 0.69	4.51 ± 0.69[d]	4.19 ± 0.62	4.23 ± 0.43	4.71 ± 0.73[c]	4.51 ± 0.52[c]
Relative liver weight (%) Females	5.95	5.88	6.57	7.04	6.10	6.32	7.14	7.44

[a]The D911P concentration in the food of F0 rats was 2.0% during the first 6 treatment weeks; reduced to 1.0% in the high-dose groups for remainder of study.
[b]Mean ± standard deviation.
[c]Significantly different from controls ($p < 0.05$) by Behrens-Fisher or Dunnett's test.
[d]Significantly different from controls ($p < 0.01$) by Behrens-Fisher or Dunnett's test.
[e]Significantly different from controls ($p < 0.05$) by Fisher's exact test.
[f]Significantly different from controls ($p < 0.001$) by Fisher's exact test.
[g]Significantly different from controls ($p < 0.01$) by Fisher's exact test.
[h]Significantly different from controls ($p < 0.05$) by Fisher's exact test performed for this review (not analyzed by authors of original study).
Source: Willoughby et al. (2000).

In contrast to the findings in males, mid- and high-dose F0 and F1 parental female rats (approximate doses of 479–623 mg/kg-day for the mid-dose groups and 1,264–1,389 mg/kg-day for the high-dose groups) exhibited significantly increased mean absolute liver weight, even when body weight was decreased in these groups (Table 5.3) (Willoughby et al., 2000). Females also showed fewer types of liver lesions (only periacinar hepatocytic vacuolation and hypertrophy) and lower incidences than males. In females, statistically significant increases in liver lesions were found only in the high-dose F0 group.

Willoughby et al. (2000) considered that the male rats exhibited a biphasic hepatic response to D911P treatment, as demonstrated by dose-related increased liver weight in male F1 and F2 pups sacrificed at postnatal day (PND) 25, but dose-related decreased liver weight and histopathological evidence of liver damage in the adult male rats sacrificed after weaning of their pups. These observations were considered by the researchers to be indicative of an initial increase in liver weight associated with hypertrophy giving way, as the animals matured, to a decrease in liver weight accompanied by degenerative lesions. The lack of liver weight decrease and milder histopathological liver lesions in the females were considered by the researchers to be evidence that the female rats were less sensitive to D911P-induced hepatotoxicity.

The lowest-observed-adverse-effect level (LOAEL) for effects on the liver in this study (Willoughby et al., 2000) is 0.5% (approximately 444–614 mg/kg-day) based on increased hepatocellular lesions (fatty vacuolation, hypertrophy, necrosis) in male rats. The corresponding no-observed-adverse-effect level (NOAEL) for liver effects in male rats is 0.1% (approximately 88–117 mg/kg-day). Female rats were less sensitive than the males, with a LOAEL of 1.0% (approximately 1,389 mg/kg-day based on the F0 generation) and a NOAEL of 0.5% (approximately 479–623 mg/kg-day) based on liver lesions.

Periportal cytoplasmic vacuolation was observed in the livers of "some" (not further specified) CFE rats administered undiluted D911P at 5 mL/kg (4,800 mg/kg based on a specific gravity of 0.96 [BASF Corporation, 2004]) by gavage once per day for 7 consecutive days (Brown et al., 1970).

Overall, animal data using D911P as a test substance supported the conclusion that there was “limited evidence” for the designation of D911P as a “hepatotoxicant.

5.9. Renal Toxicity

Data suggesting an effect of D911P on the kidney were limited to organ weight changes in the two-generation study (Willoughby et al., 2000). In males, there were small decreases in absolute kidney weight and increases in relative kidney weight in the high-dose F0 and F1 parental rats (Table 5.4). In females, body weights were not significantly different from controls and renal weights were also unchanged (a minimal 2% increase in relative kidney weight in the high-dose F1 group was reported as statistically significant, but is likely an error in the original report) (Table 5.4). The study authors stated that no organs other than the liver exhibited any macroscopic or histopathological changes considered to be related to D911P treatment. Renal samples were collected, but it was not specifically stated whether the kidneys were included in histopathological evaluations. The observed changes in kidney weights of the high-dose F0 and F1 parental rats are not considered to be of toxicological significance.

The lack of collaborating renal toxicity studies using D911P as a test substance supported the conclusion that there was "limited evidence" for the designation of D911P as a "renal toxicant."

Table 5.4. Selected Mean Organ Weights for Sprague-Dawley Rats Receiving D911P from the Diet for Two Generations								
Dietary D911P concentration (percent)	**0**	**0.1**	**0.5**	**2.0/1.0[a]**	**0**	**0.1**	**0.5**	**1.0**
Parental males	**F0**				**F1**			
Number of animals	27	28	28	28	28	28	28	27
Terminal body weight (g)	639 ± 71[b]	653 ± 70	625 ± 71	517 ± 69[c]	611 ± 72	621 ± 86	634 ± 82	538 ± 64[c]
Kidney Absolute (g)	4.33 ± 0.51	4.42 ± 0.44	4.38 ± 0.53	3.85 ± 0.52[c]	4.13 ± 0.68[d]	4.04 ± 0.53	4.31 ± 0.68	3.76 ± 0.38
Kidney Relative (%)	0.68 ± 0.05	0.68 ± 0.07	0.70 ± 0.06	0.75 ± 0.06[c]	0.67 ± 0.07[d]	0.65 ± 0.06	0.68 ± 0.07	0.70 ± 0.07[e]
Spleen Absolute (g [×10])	8.64 ± 1.32	8.85 ± 2.00	8.21 ± 1.15	7.59 ± 1.06[c]	8.64 ± 1.68	8.53 ± 1.14	8.55 ± 1.98	7.43 ± 1.27[c]
Spleen Relative (%)	0.1352	0.1355	0.1314	0.1468	0.1414	0.1374	0.1349	0.1381
Thymus Absolute (g [×10])	3.28 ± 0.65	3.27 ± 1.02	3.40 ± 1.30	3.18 ± 1.07	3.64 ± 0.96	3.71 ± 0.88	3.75 ± 1.01	3.22 ± 0.96
Thymus Relative (%)	0.0513	0.0500	0.0544	0.0615	0.0596	0.0597	0.0591	0.0599
Adrenal gland Absolute (g [×10])	0.54 ± 0.13	0.48 ± 0.15	0.47 ± 0.12	0.45 ± 0.11[e]	0.61 ± 0.12	0.56 ± 0.12	0.56 ± 0.07[e]	0.50 ± 0.08[c]
Adrenal gland Relative (%)	0.0085	0.0074	0.0075	0.0087	0.0010	0.0090	0.0088	0.0093
Parental females	**F0**				**F1**			
Number of animals	24	23	22	23	26	23	23	24
Terminal body weight (g)	351 ± 28	356 ± 27	342 ± 20	337 ± 24	341 ± 31	343 ± 34	333 ± 23	325 ± 24[c]
Kidney Absolute (g)	3.07 ± 0.38	3.02 ± 0.25	3.04 ± 0.30	2.94 ± 0.21	2.91 ± 0.36	2.77 ± 0.27	2.78 ± 0.21	2.86 ± 0.28
Kidney Relative (%)	0.88 ± 0.09	0.85 ± 0.06	0.89 ± 0.09	0.88 ± 0.07	0.86 ± 0.06	0.81 ± 0.07	0.83 ± 0.05	0.88 ± 0.07[e]
Spleen Absolute (g [×10])	6.26 ± 0.99	6.21 ± 1.06	5.83 ± 0.74	5.37 ± 0.88[c]	6.63 ± 0.92	6.36 ± 0.96	5.88 ± 0.80[c]	5.35 ± 0.72[c]
Spleen Relative (%)	0.1783	0.1744	0.1705	0.1593	0.1944	0.1854	0.1766	0.1646
Thymus Absolute (g [×10])	2.28 ± 0.59	1.97 ± 0.61	1.84 ± 0.65	1.75 ± 0.66[e]	2.50 ± 0.72	2.32 ± 0.49	2.32 ± 0.86	1.75 ± 1.14[e]
Thymus Relative (%)	0.0650	0.0553	0.0538	0.0519	0.0733	0.0676	0.0697	0.0538
Adrenal gland Absolute (g [×10])	0.88 ± 0.17	0.88 ± 0.14	0.79 ± 0.13	0.69 ± 0.13[c]	0.87 ± 0.11	0.82 ± 0.11	0.77 ± 0.11[c]	0.64 ± 0.12[c]
Adrenal gland Relative (%)	0.0251	0.0247	0.0231	0.0205	0.0255	0.0239	0.0231	0.0197

[a]The D911P concentration in the food of F0 rats was 2.0% during the first 6 treatment weeks; reduced to 1.0% in the high-dose groups for remainder of study.
[b]Mean ± standard deviation.
[c]Significantly different from controls ($p < 0.01$) by Behrens-Fisher or Dunnett's test.
[d]n=27.
[e]Significantly different from controls ($p < 0.05$) by Behrens-Fisher or Dunnett's test.
[e]Significantly different from controls ($p < 0.05$) by Fisher's exact test.

Source: Willoughby et al. (2000).

5.10. Toxicity to Lymphatic Organs

Organ weight data in the two-generation study (Willoughby et al., 2000) showed significant decreases in the absolute weights of the spleen in F0 and F1 high-dose males, and mid- (F1) and high-dose (F0, F1) females. Absolute weight decrements were dose-related. Dose-related decreases in the relative spleen weight were also seen in F0 and F1 females, but not males. Absolute thymus weights were decreased significantly in a dose-related manner in F0 and F1 females (high dose; $p < 0.05$) and substantially in high dose F0 and F1 males. Relative thymus weights were decreased in a dose-related fashion for F0 and F1 females, but not males (Table 5.4). The decreased organ weights in males are somewhat consistent with decreased body weights in these groups. However, the decreases in females occurred despite only small decreases in body weight in these groups (significant only in the high-dose F1). The study authors stated that no organs other than the liver exhibited any macroscopic or histopathological changes considered to be related to D911P treatment. Splenic and thymic tissue samples were collected, but it was not specifically stated whether they were included in histopathological evaluations. The toxicological significance of the observed decreases in spleen and thymus weights is uncertain in the absence of data on corresponding histopathological findings.

5.11. Endocrine Activity

There was no effect of D911P on estrous cyclicity or pup sexual maturation in the two-generation rat study (Willoughby et al., 2000).

Absolute adrenal weights were significantly reduced in a dose-related manner in high-dose F0 males and females and mid- and high-dose F1 males and females (Table 5.4). Calculated relative adrenal weights were not changed in F0 and F1 males, but decreased in F0 and F1 females in a dose-related fashion.. The study authors stated that no organs other than the liver exhibited any macroscopic or histopathological changes considered to be related to D911P treatment. Adrenal samples were collected, but it was not specifically stated whether they were included in histopathological evaluations. The toxicological significance of the observed decrease in absolute and relative (female) adrenal weights is uncertain in the absence of data on corresponding histopathological findings.

5.12. Reproductive Toxicity

In the two-generation rat reproduction study, D911P treatment did not affect estrous cyclicity, number mated, sex ratio, pup weight at birth, pup survival, pup gross abnormalities, or pup sexual maturation in either generation of rats (Willoughby et al., 2000). The distribution of gestation lengths was dose-related and significantly different than controls in the F0 (0.5%, $p < 0.05$; 1%, $p < 0.01$) and F1 generation rats (1%, $p < 0.001$; Table 5.5). The reduction in gestation length induced by D911P was 0.5 days. Slight dose-related decrements were reported for the number of rats pregnant, the number of live litters, the number of implantation sites, and the litter size in the F1 generation. Decrements in the above factors may be related to maternal toxicity, since final female body weights were decreased in a dose-related fashion in both the F0 and F1 generation (Table 5.6).

Significant dose-related decrements ($p <0.01$) were reported for mean pup weights in high dose F2 male and female pups at postnatal days 14 and 21. A significant decrement in mid-dose F2 female pup weight was also observed at PND 14 ($p < 0.05$; Table 5.5). Dose-related decrements were also observed in male and female F1 pup weights at PND 14 and 21.

Table 5.5. Select Reproductive Success Data for Male and Female F0 and F1 Parental Sprague-Dawley Rats Exposed to D911P in the Diet								
	F0 Male and Female Rats				**F1 Male and Female Rats**			
D911P concentration (percent in diet)	0	0.1	0.5	2.0/1.0[e]	0	0.1	0.5	1.0
Number paired (mated)	28 (27)	28 (28)	28 (28)	28 (28)	28 (28)	28 (28)	28 (27)	28 (28)
Number pregnant	26	26	26	26	28	27	26	25
Gestation length (d)	22.8 ± 0.5[b]	22.7 ± 0.4	22.5 ± 0.3[a]	22.4 ± 0.4[a]	22.6 ± 0.4	22.7 ± 0.4	22.4 ± 0.4	22.2 ± 0.3[a]
Dams littering GD 21.5	-	-	-	-	-	-	1	-
GD 22	4	3	6	9	4	3	11	15
GD 22.5	8	13	14	13	15	10	8	8
GD 23	9	8	6	2	8	12	6	1
GD 23.5 & 24	4	2	-	2	1	-	-	-
Number of live litters	25	26	26	26	28	25 (+2)	25 (+1)	24
Implantation sites	15.3 ± 3.1	15.4 ± 3.2	15.5 ± 2.0	14.8 ± 3.2	15.7 ± 2.6	13.7 ± 4.0	14.5 ± 3.5	13.9 ± 3.9
Litter size	14.3 ± 3.2	14.3 ± 3.2	14.3 ± 2.4	13.8 ± 3.4	14.4 ± 2.8	13.0 ± 3.3	13.0 ± 4.2	12.8 ± 3.0
Mean pup weight (g), **M**, PND 7	13.4 ± 3.1	13.6 ± 2.9	12.9 ± 3.4	13.6 ± 2.5	14.1 ± 2.7	14.9 ± 2.2	13.5 ± 3.3	13.5 ± 2.1
Mean pup weight (g), **M**, PND 14	32.1 ± 5.4	32.2 ± 3.8	30.5 ± 6.4	30.2 ± 3.5	33.2 ± 3.3	33.0 ± 3.1	30.4 ± 5.7	28.9 ± 2.4[c]
Mean pup weight (g), **M**, PND 21	53.4 ± 7.5	54.7 ± 5.9	52.6 ± 5.0	51.2 ± 5.2	56.0 ± 5.6	54.8 ± 5.7	51.6 ± 9.5	48.3 ± 4.1[c]
Mean pup weight (g), **F**, PND 7	13.1 ± 3.1	12.7 ± 2.7	12.7 ± 3.0	13.3 ± 2.4	13.6 ± 2.8	14.0 ± 2.3	12.9 ± 3.2	13.0 ± 2.0
Mean pup weight (g), **F**, PND 14	31.4 ± 5.5	30.8 ± 3.6	30.5 ± 3.9	29.4 ± 3.6	32.3 ± 3.6	31.6 ± 3.4	30.2 ± 3.9[d]	27.9 ± 2.7[c]
Mean pup weight (g), **F**, PND 21	51.9 ± 7.5	51.9 ± 5.4	50.5 ± 5.2	49.4 ± 4.8	53.3 ± 5.8	52.3 ± 5.3	50.6 ± 6.4	46.7 ± 4.4[c]

[a]Distribution of gestation lengths are significantly different than control ($p < 0.05 – 0.001$)
[b]Mean ± standard deviation.
[c]$p < 0.01$ when compared to control
[d]$p < 0.05$ when compared to control
[e]The D911P concentration in the food of F0 rats was 2.0% during the first 6 treatment weeks; reduced to 1.0% in the high-dose groups for remainder of study.

Source: Willoughby et al. (2000).

High-dose male rats exhibited slight, but significant organ weight changes that included decreased absolute weights of epididymides, prostate, and seminal vesicles and increased relative weights of epididymides, seminal vesicles, and testes in the F0 adults and decreased absolute (but not relative) weights of epididymides and seminal vesicles and increased relative (but not absolute) testes weight in the F1 adults (Table 5.6) (Willoughby et al., 2000).

Absolute and relative weights of the uterus and cervix combined (uterus + cervix) of high-dose F0 female rats were approximately 20% lower than those of controls ($p < 0.01$). High-dose F1 parental females showed decreases of a similar magnitude in uterus + cervix weight,

although these differences were not statistically significant. Decrements in uterus + cervix weight may be related to normal physiological variation, since an increased number of dilated uteri were observed in control groups when compared to treated groups.

Table 5.6. Select Reproductive Organ Weight Data for Male and Female F0 and F1 Parental Sprague-Dawley Rats Exposed to D911P in the Diet

	F0 Males				F1 Males			
Number of animals	27	28	28	28	28	28	28	27
Final body weight (g)	639 ± 71[b]	653 ± 70	625 ± 71	517 ± 69[c]	611 ± 72	621 ± 86	634 ± 82	538 ± 64[c]
Abs. organ weight (g)								
Epididymides	1.34 ± 0.12	1.32 ± 0.09	1.29 ± 0.13	1.26 ± 0.10[d]	1.32 ± 0.10	1.26 ± 0.16[e]	1.30 ± 0.09	1.23 ± 0.17[d]
Prostate (×10)	6.53 ± 1.69	6.49 ± 1.83	6.52 ± 1.77	5.55 ± 1.05[d]	6.00 ± 1.98	5.52 ± 1.39	5.79 ± 1.61	5.20 ± 1.21
Seminal vesicles	2.49 ± 0.29	2.66 ± 0.26[d]	2.56 ± 0.46	2.19 ± 0.33[c]	2.35 ± 0.30	2.36 ± 0.35[e]	2.28 ± 0.27	2.05 ± 0.28[c]
Testes	3.84 ± 0.42	3.82 ± 0.36	3.75 ± 0.40	3.75 ± 0.30	3.78 ± 0.32	3.85 ± 0.59[e]	3.75 ± 0.31	3.67 ± 0.63
Rel. organ weight (g)								
Epididymides	0.21 ± 0.02	0.20 ± 0.03	0.21 ± 0.03	0.25 ± 0.03[c]	0.22 ± 0.03	0.21 ± 0.03[e]	0.21 ± 0.03	0.23 ± 0.04
Prostate	0.10 ± 0.03	0.10 ± 0.03	0.10 ± 0.02	0.11 ± 0.02	0.09 ± 0.03	0.09 ± 0.02	0.09 ± 0.03	0.10 ± 0.03
Seminal vesicles	0.39 ± 0.05	0.41 ± 0.06	0.42 ± 0.10	0.43 ± 0.07[d]	0.39 ± 0.07	0.39 ± 0.06[e]	0.37 ± 0.05	0.39 ± 0.07
Testes	0.60 ± 0.07	0.59 ± 0.09	0.61 ± 0.08	0.73 ± 0.09[c]	0.63 ± 0.08	0.62 ± 0.12[e]	0.60 ± 0.08	0.70 ± 0.16[d]
	F0 Females				F1 Females			
Number of animals	24	23	22	23	26	23	23	24
Final body weight (g)	351 ± 28[b]	356 ± 27	342 ± 20	337 ± 24	341 ± 31	343 ± 34	333 ± 23	325 ± 24[c]
Abs. organ weight (g)								
Ovaries (×10)	1.10 ± 0.22	1.21 ± 0.20	1.11 ± 0.19	0.98 ± 0.21	1.10 ± 0.15	1.17 ± 0.16	1.11 ± 0.16	0.98 ± 0.20[f]
Uterus + cervix	0.53 ± 0.11	0.53 ± 0.11	0.53 ± 0.18	0.41 ± 0.10[c]	0.52 ± 0.13	0.46 ± 0.13	0.50 ± 0.13	0.43 ± 0.15
Rel. organ weight (g)								
Ovaries (×100)	3.15 ± 0.67	3.41 ± 0.52	3.25 ± 0.55	2.91 ± 0.60	3.19 ± 0.41	3.45 ± 0.49	3.34 ± 0.41	3.02 ± 0.50[f]
Uterus + cervix	0.15 ± 0.03	0.15 ± 0.04	0.16 ± 0.06	0.12 ± 0.03[c]	0.15 ± 0.04	0.15 ± 0.04	0.15 ± 0.04	0.13 ± 0.05

[a]The D911P concentration in the food of F0 rats was 2.0% during the first 6 treatment weeks; reduced to 1.0% in the high-dose groups for remainder of study.
[b]Mean ± standard deviation.
[c]Significantly different from controls ($p < 0.01$) by Behrens-Fisher or Dunnett's test.
[d]Significantly different from controls ($p < 0.05$) by Behrens-Fisher or Dunnett's test.
[e]n=27.
[f]n=23.

Source: Willoughby et al. (2000).

Pup sexual maturation (preputial separation) was slightly delayed (by one day) in the F1 pups treated with the highest dose of D911P, but the difference was not statistically significant or outside the range of historical controls. Differences in maturation may have been related to observed body weight decrements. Spermatid counts in all treated groups were significantly higher than controls in the F0 generation. Pathological findings included a slight dose-related increase in the number of small epididymides (0/28, 0/28, 1/28, 2/28; control, low-, mid-, high-dose) and small, dark, flaccid testes (0/28, 0/28, 1/28, 2/28; control, low-, mid-, high-dose) in the

F0 generation. A dose-related decrease in the number of dilated uterine glands (F0) and dilated uteri (F0, F1) was also reported.

Histopathological evaluations of reproductive organs and tissues from F0 and F1 male and female rats and additional testicular and epididymal assessments of sperm count and quality in F0 and F1 males revealed no additional evidence of treatment-related effects.

In summary, exposure of male and female Sprague-Dawley rats to D911P at up to 1% in the diet for two generations did not affect sexual behavior, fertility, or fecundity in the absence of maternal toxicity (Willoughby et al., 2000). The distribution of gestation lengths was treatment dose-related and significantly different than controls in the F0 (0.5%, $p < 0.05$; 1%, $p < 0.01$) and F1 generation rats (1%, $p < 0.001$; Table 5.5). The reduction in gestation length induced by D911P was 0.5 days. Slight (statistically insignificant) dose-related decrements were reported for the number of live litters, the number of implantation sites, and the litter size in the F1 generation. Significant decrements ($p < 0.01$) were reported for mean pup weights in high dose male and female pups at postnatal days 14 and 21. A significant decrement in female pup weight was also observed at PND 14 ($p < 0.05$).

Histopathological assessments revealed no treatment-related effects on reproductive organs in males or females. There were no effects on estrous cyclicity or sperm parameters. High-dose male rats exhibited slight, but significant organ weight changes that included decreased absolute weights of epididymides, prostate, and seminal vesicles and increased relative weights of epididymides, seminal vesicles, and testes in the F0 adults and decreased absolute (but not relative) weights of epididymides and seminal vesicles and increased relative (but not absolute) testes weight in the F1 adults (Table 5.6) (Willoughby et al., 2000). The slight changes in reproductive organ weights in the F0 and F1 males may reflect treatment-related effects on body weight. Therefore, for the parental male rats, the 1% D911P dietary level (approximate dose of 1,238–1,510 mg/kg-day) is a NOAEL for reproductive effects.

In contrast to the organ weight changes in males, the observed decreases in absolute and relative uterus + cervix weights in parental females do not appear to be a simple reflection of altered body weights. Absolute and relative weights of the uterus + cervix of high-dose F0 female rats were approximately 20% lower than those of controls ($p < 0.01$). For parental female rats, the 1% D911P dietary level (approximate dose of 1,264–1,389 mg/kg-day) is a LOAEL for reproductive effects and the 0.5% D911P dietary level (approximate dose of 479–623 mg/kg-day) is a NOAEL for reproductive effects.

The lack of corroborating reproductive toxicity studies using D911P as a test substance supported the conclusion that there was "limited evidence" for the designation of D911P as a "reproductive toxicant".

5.13. Prenatal, Perinatal, and Post-natal Toxicity

In the two-generation study (Willoughby et al., 2000), high-dose F2 male and female pups exhibited significantly lower body weights than respective controls during PNDs 14–25 (Table 5.7). Although this effect was also observed in mid-dose F2 female pups at PND 14, it was not seen at other PND time points in this group. The D911P treatment-related effects on pup body weight occurred at doses that also resulted in depressed mean maternal body weight during the lactation period and may indicate an effect on the milk production in underweight lactating dams. However, the effects on pup body weight were not seen during the early lactation period and became evident during the latter stages of the lactation period, during which time the pups were beginning to consume solid food, which provides support to a possible systemic toxicity effect in the pups, particularly in light of the finding that the effect persisted for 4 days following the termination of lactation. There were no indications of D911P treatment-related effects on other developmental parameters assessed, including pup survival, or pup gross abnormalities. Pup sexual maturation (preputial separation) was slightly delayed (by one day) in the highest dose of D911P, but the difference was not statistically significant. Based on the lack of apparent D911P treatment-related developmental toxicity, the 1% D911P dietary level (approximate doses of 1,238–1,510 and 1,264–1,389 mg/kg-day for the parental males and females, respectively) is a NOAEL for developmental effects.

Table 5.7. Results of Body Weight Assessments in Two Generations of Sprague-Dawley Rat Pups Whose Parents Were Exposed to D911P in the Diet								
Dietary D911P concentration (percent)	**0**	**0.1**	**0.5**	**2.0/1.0[a]**	**0**	**0.1**	**0.5**	**1.0**
Male pup body weight (g)[b]	**F1**				**F2**			
PND 1	6.1 ± 0.8[c]	6.2 ± 0.9	6.3 ± 0.7	6.4 ± 0.6	6.2 ± 0.7	6.6 ± 0.7	6.4 ± 1.0	6.5 ± 0.6
PND 7	13.4 ± 3.1	13.6 ± 2.9	12.9 ± 3.4	13.6 ± 2.5	14.1 ± 2.7	14.9 ± 2.2	13.5 ± 3.3	13.5 ± 2.1
PND 14	32.1 ± 5.4	32.3 ± 3.8	30.5 ± 6.4	30.2 ± 3.5	33.2 ± 3.3	33.0 ± 3.1	30.4 ± 5.7	28.9 ± 2.4[d]
PND 21	53.4 ± 7.5	54.7 ± 5.9	52.6 ± 5.0	51.2 ± 5.2	56.0 ± 5.6	54.8 ± 5.7	51.6 ± 9.5	48.3 ± 4.1[d]
PND 25[f]	70.2 ± 10.4	70.6 ± 7.7	69.8 ± 7.7	67.8 ± 8.1	73.3 ± 7.2	71.8 ± 6.6	70.1 ± 8.9	64.4 ± 5.2[d]
Female pup body weight (g)[b]	**F1**				**F2**			
PND 1	5.7 ± 0.7	5.8 ± 0.7	5.9 ± 0.6	6.0 ± 0.7	5.8 ± 0.6	6.1 ± 0.7	6.2 ± 0.9	6.2 ± 0.6
PND 7	13.1 ± 3.1	12.7 ± 2.7	12.7 ± 3.0	13.3 ± 2.4	13.6 ± 2.8	14.0 ± 2.3	12.9 ± 3.2	13.0 ± 2.0
PND 14	31.4 ± 5.5	30.8 ± 3.6	30.5 ± 3.9	29.4 ± 3.6	32.3 ± 3.6	31.6 ± 3.4	30.2 ± 3.9[e]	27.9 ± 2.7[d]
PND 21	51.9 ± 7.5	51.9 ± 5.4	50.5 ± 5.2	49.4 ± 4.8	53.3 ± 5.8	52.3 ± 5.3	50.6 ± 6.4	46.7 ± 4.4[d]
PND 25[f]	66.4 ± 11.0	66.3 ± 7.4	65.8 ± 7.7	64.1 ± 6.3	68.7 ± 7.5	66.9 ± 6.2	66.0 ± 8.2	60.6 ± 5.4[d]

[a]The D911P concentration in the food of F0 rats was 2.0% during the first 6 treatment weeks; reduced to 1.0% in the high-dose groups for remainder of study.
[b]Numbers of pups contributing to the mean pup body weight data were not provided in the study report.
[c]Mean ± standard deviation; mean body weights were determined from those surviving pups not destined for mating.
[d]Significantly different from controls ($p < 0.01$) by Behrens-Fisher or Dunnett's test.
[e]Significantly different from controls ($p < 0.05$) by Behrens-Fisher or Dunnett's test.

Source: Willoughby et al. (2000).

In the developmental toxicity study in rats conducted by Fulcher et al. (2001), pre- and post-implantation losses were unaffected by D911P treatment. There were no significant treatment-related effects on resorbed litters, number of live litters, gravid uterus weight, number of corpora lutea, number of implantation sites/dam, number of resorptions/dam, sex ratio, placental weight, litter weight, or percentages of litters with gross abnormalities. Fetal body weights were slightly increased in high dose males and overall, and significantly increased in high dose females (Table 5.8). Visceral and skeletal examinations of fetuses revealed significantly increased numbers of high-dose fetuses/litter exhibiting dilated renal pelvis and significantly increased numbers of mid- and high-dose fetuses/litter with supernumerary lumbar ribs (Table 5.8). Significantly positive trend tests were also reported for each variation. Treatment-related increases in the numbers of cervical ribs or complete 14th ribs were not demonstrated in this study (on a litter or fetus-basis; data not shown). This study identified a NOAEL of 250 mg/kg-day and a LOAEL of 500 mg/kg-day for developmental effects based on increased incidence of supernumerary lumbar ribs in the fetuses of rat dams administered D911P by gavage during gestation.

Table 5.8. Selected Fetal Observations Following Administration of D911P to Sprague-Dawley Rat Dams by Gavage During Gestation (GDs 1–19)				
	D911P dose (mg/kg-d)			
	0	250	500	1,000
Fetal weight – females (g ± SD)	3.53 ± 0.22	3.66 ± 0.21	3.60 ± 0.22	3.72 ± 0.20[d]
Fetal weight – males (g ± SD)	3.78 ± 0.23	3.86 ± 0.19	3.82 ± 0.27	3.93 ± 0.26
Fetal weight – comb. M&F (g ± SD)	3.66 ± 0.21	3.76 ± 0.20	3.70 ± 0.23	3.83 ± 0.22
Fetal Exams				
Fetuses examined Litters examined	168 22	158 22	158 22	157 21
Dilated renal pelvis Number of fetuses Number of litters Percent affected fetuses per litter	 2 2 1	 7 3 4.1	 2 1 1.3	 12 5 7.9[a,b]
Supernumerary lumbar ribs Number of fetuses Number of litters Percent affected fetuses per litter	 23 13 13.6	 24 10 15.9	 45 17 28.2[c]	 40 14 26.7[a,b]

[a]Significantly different from control ($p < 0.05$), according to Wald χ^2 test.
[b]Significant for trend ($p < 0.01$) using logistic regression.
[c]Significantly different from control ($p < 0.01$), according to Wald χ^2 test.
[d]Significantly different from control ($p < 0.01$).

Source: Fulcher et al. (2001).

The lack of additional developmental toxicity studies that support and/or corroborate the above results supported the conclusion that there was "limited evidence" for the designation of D911P as a "developmental toxicant".

5.14. Carcinogenicity

The lack of comprehensive carcinogenicity, genotoxicity, or initiation/promotion studies using only D911P as a test substance supported the conclusion that there was "inadequate evidence" for the designation of D911P as a "carcinogen".

Genotoxicity

D911P was not mutagenic to *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 at concentrations up to 5,000 µg/plate either with or without metabolic activation (BASF AG, 1989, as reported in NICNAS, 2008).

Initiation and Promotion

No initiation or promotion studies were located for D911P.

Carcinogenicity Studies

No carcinogenicity studies were located for D911P.

6. EXPOSURE

Exposure to HMWPEs is believed to occur primarily in the workplaces where they are manufactured. The primary workplace exposure in manufacturing activities would be dermal and there may be a potential for formation of aerosol during some applications (OECD, 2004). Because HMWPEs are handled only in industrial manufacturing facilities and manufacture involves incorporation of the phthalate ester into a matrix, minimal consumer exposure is expected (OECD, 2004). The consumer is exposed indirectly through use of the products that may contain the HMWPEs and uptake is expected to be low (OECD, 2004). Exposure data specific to D911P were not found.

7. DISCUSSION

Overall Uncertainty

The hazard database for D911P consisted primarily of two well described studies, a two generation reproduction study, and a developmental study. Additional studies described acute effects and genotoxicity.

Appendix A provides a summary of the NOAELs and LOAELs for organ-specific endpoints for D911P, which were derived from a study of Sprague-Dawley rats administered D911P in the diet for two generations (Willoughby et al., 2000), a developmental toxicity study in which Sprague-Dawley rat dams were administered D911P by gavage on GDs 1–19 (Fulcher et al., 2001), and a very limited 7-day repeated-dose oral study (Brown et al., 1970). The report by Willoughby et al. (2000) included only limited investigation of endpoints related to anti-androgen activity; there was a slight effect on male sexual maturation, as reflected by a delay of preputial separation, in this study. However, related endpoints, such as anogenital distance and nipple retention, which may be more sensitive, were not monitored. This limitation should be

taken into account when comparing developmental endpoints for D911P with similar endpoints for other phthalate esters**.**

Overall Acceptable Daily Intakes

Acceptable daily intakes values (ADI's) are calculated when a given chemical is considered "toxic" and sufficient toxicity information is available. The ADI is the amount of a chemical that one may be exposed to on a daily basis without posing a significant risk of health effects to consumers. ADI's were not estimated for D911P relevant exposure durations for the general population or for other sensitive subpopulations because confirmatory data on toxicological endpoints were not available.

8. REFERENCES

BASF AG. (1971). Unpublished report. Abteilung Toxikologie Untersuchung (XXI/17), 23.03.1971 (as cited in European Commission, 2000, NICNAS, 2008)

BASF AG. (1989). Unpublished report. Abteilung Toxikologie Untersuchung (88/576), 24.02.1989 (as cited in NICNAS, 2008)

BASF Corporation. (2009) Palatinol 911P. Safety data sheet. Available online at http://www.sterlingchemicals.com/operations/MSDS-BASF-Palatinol911P.pdf (accessed December 28, 2010).

Bizzari, S.N., Blagoev, M., and A. Kishi. (2007) CEH Marketing Research Report. Plasticizers. SRI Consulting. 148pp.

Bizzari, S.N., Blagoev, M., and A. Kishi. (2009) CEH Marketing Research Report. Plasticizers. SRI Consulting. 169pp.

Brown, VK; Muir, CM; Thorpe, E. (1970) A contribution to the toxicology of some alcohol mixtures containing 7 to 9 and 9 to 11 carbon atoms and the corresponding phthalate esters. Arch Toxikol 26(1):84–90.

European Commission. (2000) Substance ID: 68515-43-5. 1,2-Benzenedicarboxylic acid, di C9-11-branched and linear alkyl esters. IUCLID Dataset. European Commission. European Chemicals Bureau. Available online at http://ecb.jrc.ec.europa.eu/esis/index.php?PGM=dat (accessed October 12, 2010).

ExxonMobil. 2001. Jayflex plasticizers; Sales specifications, Jayflex L911P plasticizer Di (nonyl, undecyl) phthalate. http://www.exxonmobilchemical.com/Chem-English/Files/Resources/oxo_jayflex_l911p_na_en-fps.pdf.

Godwin A. (2010) Uses of phthalates and other plasticizers. ExxonMobil Chemical Company. Available on line at: http://www.cpsc.gov/about/cpsia/chap/godwin.pdf.

Fulcher, SM; Willoughby, CR; Heath, JA; et al. (2001) Developmental toxicity of di-(C(7)-C(9) alkyl) phthalate and di-(C(9)-C(11) alkyl) phthalate in the rat. Reprod Toxicol 15(1):95–102.

NICNAS. (2008) Di-C9-11-alkyl phthalate. Existing chemical hazard assessment report. National Industrial Chemicals Notification and Assessment Scheme. Australian Government. Available online at http://www.nicnas.gov.au/Publications/CAR/Other/DiC9-11%20PE%20hazard%20assessment.pdf (accessed October 15, 2010).

OECD (Organisation for Economic Cooperation and Development). (2004) SIDS initial assessment report for SIAM 19: Category high molecular weight phthalate esters. October 2004.

POLYNT S.p.A.. 2011. Diplast® L 9-11, plasticizers for PVC. http://eng.polynt.it/user/Default.aspx?MOD=PRD&SEZ=2#

U.S. EPA. (2010) Hazard characterization document-screening-level hazard characterization. phthalate esters. U. S. Environmental Protection Agency, April 2010.

Willoughby, CR; Fulcher, SM; Creasy, DM; et al. (2000) Two-generation reproduction toxicity studies of di-(C(7)-C(9) alkyl) phthalate and di-(C(9)-C(11) alkyl) phthalate in the rat. Reprod Toxicol 14(5):427–450.

Appendix A. Summary of Endpoints by Organ System

Table A.1. Summary of NOAELs/LOAELs Identified for D911P by Organ System

Species (Gender)	Exposure Route	Dose (Number of Animals per Dose Group)	Dose Duration	Effect Category	Toxicological Endpoint	Toxicological Basis	Citation
CFE rat (M&F)	Gavage	0, 4,800 mg/kg-d (20 controls/sex; 8 D911P-dosed rats/sex)	Daily for 7 days	Death	NOAEL=4,800 mg/kg-day	No deaths	Brown et al., 1970
				General	LOAEL=4,800 mg/kg-day	"General depression"	
				Liver	LOAEL=4,800 mg/kg-day	Periportal cytoplasmic vacuolation in "some" rats	
Sprague-Dawley rat (M&F)	Dietary (0, 0.1, 0.5, or 1.0% in food for two generations)	Approximate doses to parental males: 0, 88–117, 444–614, 1,238–1,510 mg/kg-day Approximate doses to parental females: 0, 94–120, 479–623, 1,264–1,389 mg/kg-day (F0: 24–28/group; F1 parental: 28/group)	10 weeks prior to mating, up to 3 weeks of mating and throughout gestation and lactation (2 weeks of lactation for parental males, until weaning at PND 21 for parental females)	Mortality	NOAEL=1,238–1,510 mg/kg-day	No treatment-related deaths	Willoughby et al., 2000
				General	NOAEL=444–614 mg/kg-day LOAEL=1,238–1,510 mg/kg-day	Decreased body weight in parental males	
				Liver	NOAEL=88–117 mg/kg-day LOAEL=444–614 mg/kg-day	Increased incidences of liver lesions in parental males	
				Kidney	NOAEL=1,238–1,510 mg/kg-day	No toxicologically significant effects	
				Lymphatic organs	NOAEL=1,238–1,510 mg/kg-day	Organ weight decreases of uncertain toxicological significance in spleen and thymus	
				Endocrine activity	NOAEL=1,238–1,510 mg/kg-day	Organ weight decreases of uncertain toxicological significance in adrenal gland; no effect on estrous cyclicity or pup sexual maturation	
				Reproduction	Parental males: NOAEL=1,238–1,510 mg/kg-day Parental females: NOAEL=479–623 mg/kg-day LOAEL=1,264–1,389 mg/kg-day	No toxicologically significant effects in parental males; decreased absolute and relative uterus + cervix weight in parental females; no effects on male or female reproductive success	
				Development/ fetus	NOAEL=1,238–1,510 mg/kg-day	No toxicologically significant effects	

Table A.1. Summary of NOAELs/LOAELs Identified for D911P by Organ System							
Species (Gender)	**Exposure Route**	**Dose (Number of Animals per Dose Group)**	**Dose Duration**	**Effect Category**	**Toxicological Endpoint**	**Toxicological Basis**	**Citation**
Sprague-Dawley rat (F)	Gavage in olive oil	0, 250, 500, 1,000 mg/kg-day (13/group)	Once daily on GDs 1–19	Mortality	NOAEL=1,000 mg/kg-day	No treatment-related deaths	Fulcher et al., 2001
				General	NOAEL=1,000 mg/kg-day	No toxicologically significant maternal effects	
				Development/ fetus	NOAEL=250 mg/kg-day LOAEL=500 mg/kg-day	Increased incidence of fetal supernumerary ribs	

Appendix B. Critical Study Reviews

Willoughby et al. (2000)

The systemic and reproductive toxicity of D911P was assessed in a study of Sprague-Dawley rats (28/sex/group) administered D911P (purity 99.2%) in the diet at concentrations of 0, 0.1, 0.5, or 1.0% for two generations (Willoughby et al., 2000). The high-dose group initially received D911P at 2.0%; however, the concentration was reduced to 1.0% after the sixth week of treatment due to concern regarding body weights in the high-dose males (see below). Animals were observed daily for clinical signs, and body weights and food consumption were periodically measured. Treatment of the F0 generation was initiated 10 weeks prior to mating. Estrous cyclicity was assessed for 10 days prior to pairing; D911P treatment continued throughout mating, gestation, and lactation. Mated pairs were observed for copulations and fertility; pregnant females were observed for reproductive success and pups were evaluated for body weight, viability, and external and visceral malformations through day 4 of lactation. On PND 4, offspring from the F0 matings were culled to four males and four females per litter where possible. At PND 25, one male and one female from each available litter were randomly selected to produce a second generation of pups. The selected F1 males and females were examined daily for preputial separation (starting on PND 38) or vaginal opening (starting on PND 28); body weight was recorded on the day separation or opening was completed. D911P treatment of the F1 parental rats continued in the same manner as that of the corresponding F0 rats, and the same endpoints were monitored through mating, gestation, and lactation.

For both generations, when the majority of litters reached 2 weeks of age, the parental males were sacrificed, the epididymides were removed and weighed, and fluid from the cauda was assessed for sperm count, motility, and morphology (Willoughby et al., 2000). Sperm counts were also made from testicular tissue samples. At weaning of their pups, the parental females were sacrificed and uteri were examined for number of implantation sites. Parental rats of both generations were subjected to gross and histopathologic evaluations of major organs and tissues. First-generation pups not selected for continuation and all second generation pups were sacrificed at PND 25 and examined for gross and histopathologic abnormalities. At necropsy, livers from five of the F1 parental males were homogenized for evaluation of protein content and cyanide-insensitive palmitoyl CoA oxidase activity (a marker of peroxisomal proliferation).

The study authors (Willoughby et al., 2000) presented graphical information regarding body weight, food consumption, and food efficiency, and estimated D911P intakes at selected

times during the treatment periods. The author-reported time point dose estimates are summarized in Table B.1, along with averages for the premating, gestation, lactation, and overall treatment periods calculated for this review. The study authors noted that doses to the F0 and F1 males and females decreased during the 10 weeks of treatment prior to pairing as the animals grew, and that the F0 and F1 females exhibited increasing D911P intake during the first 2 weeks of lactation, reflecting increased food consumption during this period as demand from the litter increased.

Table B.1. Test Chemical Intake by Sprague-Dawley Rats Administered D911P in the Diet for Two Generations, as Reported by the Study Authors Except Where Noted			
D911P concentration in food	**0.1%**	**0.5%**	**1.0%[a]**
Estimated dose F0 males			
Premating treatment week 1	120[b]	600	2,400
Premating treatment week 7	61	312	684
Premating treatment week 10	56	280	619
Average (treatment weeks 1–10)[c]	88	444	1,510
Estimated dose F0 females			
Premating treatment week 1	120	600	2,400
Premating treatment week 7	77	388	792
Premating treatment week 10	63	328	696
Average (treatment weeks 1–10)[c]	92	464	1,548
Gestation week 1	76	379	787
Gestation week 3	66	343	724
Average (gestation weeks 1–3)[c]	71	361	756
Lactation week 1	118	593	1,329
Lactation week 2	163	867	1,760
Average (lactation weeks 1 and 2)[c]	141	730	1,545
TWA dose[d]	94	479	1,389
Estimated dose adult F1 males[e]			
Premating treatment week 1	174	917	1,840
Premating treatment week 10	60	311	636
Average (treatment weeks 1–10)[c]	117	614	1,238
Estimated dose adult F1 females[e]			
Premating treatment week 1	180	910	1,858
Premating treatment week 10	72	387	781
Average (treatment weeks 1–10)[c]	126	648	1,319
Gestation week 1	86	454	859
Gestation week 3	76	411	850
Average (gestation weeks 1–3)[c]	81	432	854
Lactation week 1	123	636	1,327
Lactation week 2	174	928	1,878
Average (lactation weeks 1 and 2)[c]	148	782	1,602
TWA dose[d]	120	623	1,264

[a]The D911P concentration in the food of high-dose F0 males and females was 2.0% during the first 6 treatment weeks, and was reduced to 1.0% for remainder of study.
[b]Estimated dose in mg/kg-day.
[c]Estimated for this review by averaging the available weekly author-estimated doses during the respective treatment periods (i.e., premating treatment weeks 1 and 10, gestation weeks 1 and 3, and lactation weeks 1 and 2).
[d]Estimated for this review by TWAs for the premating, gestation, and lactation periods combined.
[e]Estimated doses for F1 parental rats receiving dietary D911P after weaning.

TWA = time-weighted average

Source: Willoughby et al. (2000).

No clinical signs of toxicity were reported (Willoughby et al., 2000). Body weight and food consumption were significantly reduced relative to controls in high-dose F0 males throughout the study. Mean body weight in high-dose F0 male rats was significantly ($p < 0.01$)

lower than that of controls by the end of treatment week 1; it was as much as 25% lower than controls after 6 weeks of D911P exposure. Although the concentration of D911P in the diet was reduced from 2 to 1% after treatment week 6, the effect on body weight persisted; at terminal sacrifice, after approximately 18 weeks of D911P exposure, mean body weight of the high-dose F0 males was 19% lower than controls (see Table B.2). The depressed body weight in the high-dose F0 males was accompanied by reduced food intake, which steadily declined after premating treatment week 2 to approximately 85% of the food intake of controls by the end of treatment week 10. Mean body weight in high-dose F1 parental male rats was also significantly lower than that of controls, beginning at the end of treatment week 5, and as much as 12% lower than controls at terminal sacrifice (Table B.2). High-dose F1 parental male rats consumed slightly less food than controls, but the difference was not statistically significant. There were no effects on body weight or food consumption in F0 or F1 parental male rats treated with lower doses of D911P.

Mean body weights in high-dose F0 females were statistically lower than controls from treatment weeks 5–10 premating, although the magnitude of the change from control was small (<10% lower; $p < 0.05$) (Willoughby et al., 2000). No change was seen at lower doses. In the F1 parental females, D911P did not affect body weights during the premating treatment period. Mean body weights of high-dose F0 and mid- and high-dose F1 parental females were significantly lower than those of controls after gestation week 1, but not significantly different from controls after gestation weeks 2 and 3. High-dose F0 females exhibited significantly lower mean body weight than that of controls on PNDs 7 and 14 ($p < 0.01$), but not on PND 21. In the F1 parental females, significantly lower mean body weights were observed at the mid-dose level on PNDs 4, 7, and 14 ($p < 0.05$), and at the high-dose level on PNDs 4 and 7 ($p < 0.05$) and PNDs 14 and 21 ($p < 0.01$). The magnitude of the body weight differences during gestation and lactation did not exceed 10%. Mean body weights of D911P-treated F0 female rats were not significantly different from controls at terminal sacrifice (Table B.2). The mean terminal body weight of the high-dose F1 parental females was 5% lower than that of controls ($p < 0.05$); there were no differences from controls at lower doses (Table B.2). Food consumption was similar for all female treatment groups of both parental generations throughout the study.

Table B.2. Results of Body Weight Assessments in Sprague-Dawley Rats Exposed to D911P in the Diet for Two Generations								
Dietary D911P concentration (percent)	**0**	**0.1**	**0.5**	**2.0/1.0[a]**	**0**	**0.1**	**0.5**	**1.0**
Parental males	**F0**				**F1**			
Number of animals	27	28	28	28	28	28	28	27
Terminal body weight (g)	639 ± 71[b]	653 ± 70	625 ± 71	517 ± 69[c]	611 ± 72	621 ± 86	634 ± 82	538 ± 64[c]
Parental females	**F0**				**F1**			
Number of animals	24	23	22	23	26	23	23	24
Terminal body weight (g)	351 ± 28[b]	356 ± 27	342 ± 20	337 ± 24	341 ± 31	343 ± 34	333 ± 23	325 ± 24[d]
Male pup body weight (g)[e]	**F1**				**F2**			
PND 1	6.1 ± 0.8	6.2 ± 0.9	6.3 ± 0.7	6.4 ± 0.6	6.2 ± 0.7	6.6 ± 0.7	6.4 ± 1.0	6.5 ± 0.6
PND 7	13.4 ± 3.1	13.6 ± 2.9	12.9 ± 3.4	13.6 ± 2.5	14.1 ± 2.7	14.9 ± 2.2	13.5 ± 3.3	13.5 ± 2.1
PND 14	32.1 ± 5.4	32.3 ± 3.8	30.5 ± 6.4	30.2 ± 3.5	33.2 ± 3.3	33.0 ± 3.1	30.4 ± 5.7	28.9 ± 2.4[c]
PND 21	53.4 ± 7.5	54.7 ± 5.9	52.6 ± 5.0	51.2 ± 5.2	56.0 ± 5.6	54.8 ± 5.7	51.6 ± 9.5	48.3 ± 4.1[c]
PND 25[f]	70.2 ± 10.4	70.6 ± 7.7	69.8 ± 7.7	67.8 ± 8.1	73.3 ± 7.2	71.8 ± 6.6	70.1 ± 8.9	64.4 ± 5.2[c]
Female pup body weight (g)[e]	**F1**				**F2**			
PND 1	5.7 ± 0.7	5.8 ± 0.7	5.9 ± 0.6	6.0 ± 0.7	5.8 ± 0.6	6.1 ± 0.7	6.2 ± 0.9	6.2 ± 0.6
PND 7	13.1 ± 3.1	12.7 ± 2.7	12.7 ± 3.0	13.3 ± 2.4	13.6 ± 2.8	14.0 ± 2.3	12.9 ± 3.2	13.0 ± 2.0
PND 14	31.4 ± 5.5	30.8 ± 3.6	30.5 ± 3.9	29.4 ± 3.6	32.3 ± 3.6	31.6 ± 3.4	30.2 ± 3.9[d]	27.9 ± 2.7[c]
PND 21	51.9 ± 7.5	51.9 ± 5.4	50.5 ± 5.2	49.4 ± 4.8	53.3 ± 5.8	52.3 ± 5.3	50.6 ± 6.4	46.7 ± 4.4[c]
PND 25[f]	66.4 ± 11.0	66.3 ± 7.4	65.8 ± 7.7	64.1 ± 6.3	68.7 ± 7.5	66.9 ± 6.2	66.0 ± 8.2	60.6 ± 5.4[c]

[a]The D911P concentration in the food of F0 rats was 2.0% during the first 6 treatment weeks; reduced to 1.0% in the high-dose groups for remainder of study.
[b]Mean ± standard deviation.
[c]Significantly different from controls ($p < 0.01$) by Behrens-Fisher or Dunnett's test.
[d]Significantly different from controls ($p < 0.05$) by Behrens-Fisher or Dunnett's test.
[e]Numbers of pups contributing to the mean pup body weight data were not provided in the study report.
[f]Mean body weights were determined from those surviving pups not destined for mating.

Source: Willoughby et al. (2000).

In the two-generation rat reproduction study, D911P treatment did not affect estrous cyclicity, number mated, sex ratio, pup weight at birth, pup survival, pup gross abnormalities, or pup sexual maturation in either generation of rats (Willoughby et al., 2000). The distribution of gestation lengths was dose-related and significantly different than controls in the F0 (0.5%, $p < 0.05$; 1%, $p < 0.01$) and F1 generation rats (1%, $p < 0.001$; Table B3). The reduction in gestation length induced by D911P was 0.5 days. Slight dose-related decrements were reported for the number of rats pregnant, the number of live litters, the number of implantation sites, and the litter size in the F1 generation. Decrements in the above factors may be related to maternal toxicity, since final female body weights were decreased in a dose-related fashion in both the F0 and F1 generation (Table B2).

Table B3. Select Reproductive Success Data for Male and Female F0 and F1 Parental Sprague-Dawley Rats Exposed to D911P in the Diet

	F0 Male and Female Rats				F1 Male and Female Rats			
D911P concentration (percent in diet)	0	0.1	0.5	2.0/1.0[c]	0	0.1	0.5	1.0
Number paired (mated)	28 (27)	28 (28)	28 (28)	28 (28)	28 (28)	28 (28)	28 (27)	28 (28)
Number pregnant	26	26	26	26	28	27	26	25
Gestation length (d)	22.8 ± 0.5[b]	22.7 ± 0.4	22.5 ± 0.3[a]	22.4 ± 0.4[a]	22.6 ± 0.4	22.7 ± 0.4	22.4 ± 0.4	22.2 ± 0.3[a]
Dams littering GD 21.5	-	-	-	-	-	-	1	-
GD 22	4	3	6	9	4	3	11	15
GD 22.5	8	13	14	13	15	10	8	8
GD 23	9	8	6	2	8	12	6	1
GD 23.5 & 24	4	2	-	2	1	-	-	-
Number of live litters	25	26	26	26	28	25 (+2)	25 (+1)	24
Implantation sites	15.3 ± 3.1	15.4 ± 3.2	15.5 ± 2.0	14.8 ± 3.2	15.7 ± 2.6	13.7 ± 4.0	14.5 ± 3.5	13.9 ± 3.9
Litter size	14.3 ± 3.2	14.3 ± 3.2	14.3 ± 2.4	13.8 ± 3.4	14.4 ± 2.8	13.0 ± 3.3	13.0 ± 4.2	12.8 ± 3.0

[a]Distribution of gestation lengths are significantly different than control ($p < 0.05 – 0.001$)
[b]Mean ± standard deviation.
[c]The D911P concentration in the food of F0 rats was 2.0% during the first 6 treatment weeks; reduced to 1.0% in the high-dose groups for remainder of study.

Source: Willoughby et al. (2000).

Mean body weight data for F1 and F2 pups at selected postnatal time points are included in Table B.2. There were no significant differences in body weights between controls and D911P treatment groups of F1 pups at any time point through PND 25 or among F2 pups at PNDs 1 or 7.

Significantly lower mean body weight ($p < 0.05$) was noted in mid-dose F2 female pups at PND 14 (7% lower than controls), but not at PND 21. High-dose F2 male and female pups

exhibited significantly lower mean body weights (12–14% lower than respective controls) at PNDs 14 and 21 ($p < 0.01$), and this effect persisted through sacrifice at PND 25.

Upon sacrifice, study animals were evaluated for organ weights and histopathology, as reported above (Willoughby et al., 2000). Data relating to effects of D911P on the liver are shown in Table B.4. The study authors provided absolute (but not relative) liver weight data for parental male and female rats of both generations and for F1 and F2 weanlings that were sacrificed at PND 25. High-dose F0 and F1 parental male rats exhibited significantly decreased mean absolute liver weights; the decreases correlate roughly with the observed decreases in body weight in these same groups. Lesions of the periacinar hepatocytes (fatty vacuolation, hypertrophy, necrosis) were significantly increased in a dose-related fashion in mid- and high-dose F0 and F1 parental male rats. Additional lesions observed at increased incidences in the high-dose males were regenerative hyperplasia, bile duct proliferation, and clear cell, basophilic, and eosinophilic foci. Evaluations of livers from mid- and high-dose F1 males revealed significantly increased palmitoyl CoA oxidase activity suggestive of a treatment-related peroxisomal proliferative effect; the high-dose group exhibited nearly 2-fold higher palmitoyl CoA oxidase activity than that of controls.

Table B.4. Results of Liver Evaluations for Sprague-Dawley Rats Receiving D911P from the Diet for Two Generations								
Dietary D911P concentration (percent)	**0**	**0.1**	**0.5**	**2.0/1.0[a]**	**0**	**0.1**	**0.5**	**1.0**
Parental males	**F0**				**F1**			
Number of animals assessed for liver weight	27	28	27	28	28	28	28	26
Absolute liver weight (g)	24.2 ± 4.5[b]	24.7 ± 3.5	24.3 ± 4.0	20.7 ± 6.0[c]	23.5 ± 4.2	24.1 ± 4.4	25.9 ± 6.9	19.9 ± 3.4[d]
Incidences of histopathologic liver lesions:								
Regenerative hyperplasia	0/28	0/7	0/11	7/28[e]	0/28	0/3	0/12	18/28[f]
Bile duct proliferation	0/28	0/7	1/11	24/28[f]	1/28	0/3	1/12	23/28[f]
Clear cell foci	0/28	0/7	1/11	24/28[f]	0/28	0/3	0/12	13/28[f]
Basophilic foci	0/28	0/7	1/11	22/28[f]	0/28	0/3	0/12	16/28[f]
Eosinophilic foci	0/28	0/7	0/11	8/28[g]	0/28	0/3	0/12	3/28
Periacinar hepatocytes:								
Fatty vacuolation	0/28	0/7	9/11[h]	23/28[f]	2/28	0/3	8/12[h]	18/28[f]
Hypertrophy	0/28	1/7	5/11[h]	20/28[f]	0/28	0/3	5/12[h]	24/28[f]
Necrosis	0/28	0/7	3/11[h]	28/28[f]	0/28	0/3	3/12[h]	25/28[f]
Pigment	0/28	0/7	0/11	1/28	0/28	0/3	0/12	10/28[f]
Parental females	**F0**				**F1**			
Number of animals assessed for liver weight	24	23	22	23	26	23	23	24
Absolute liver weight (g)	19.9 ± 2.5[b]	20.9 ± 2.6	24.3 ± 1.8[d]	25.1 ± 2.1[d]	20.5 ± 2.7	20.9 ± 2.7	23.4 ± 2.6[d]	25.2 ± 2.6[d]
Incidences of histopathologic liver lesions								
Periacinar hepatocytic fatty vacuolation	0/28	0/2	1/5	8/28[g]	0/28	0/2	3/11	4/28
Periacinar hepatocytic hypertrophy	0/28	0/2	0/5	7/28[e]	0/28	0/2	2/11	2/28
Offspring sacrificed at PND 25	**F0**				**F1**			
Absolute liver weight (g)								
Males	4.27 ± 0.80[b]	4.23 ± 0.53	4.64 ± 0.74	4.95 ± 0.82[c]	4.36 ± 0.55	4.47 ± 0.48	4.88 ± 0.83[d]	4.69 ± 0.54[d]
Females	3.95 ± 0.75	3.90 ± 0.59	4.32 ± 0.69	4.51 ± 0.69[d]	4.19 ± 0.62	4.23 ± 0.43	4.71 ± 0.73[c]	4.51 ± 0.52[c]

[a]The D911P concentration in the food of F0 rats was 2.0% during the first 6 treatment weeks; reduced to 1.0% in the high-dose groups for remainder of study.
[b]Mean ± standard deviation.
[c]Significantly different from controls ($p < 0.05$) by Behrens-Fisher or Dunnett's test.
[d]Significantly different from controls ($p < 0.01$) by Behrens-Fisher or Dunnett's test.
[e]Significantly different from controls ($p < 0.05$) by Fisher's exact test.
[f]Significantly different from controls ($p < 0.001$) by Fisher's exact test.
[g]Significantly different from controls ($p < 0.01$) by Fisher's exact test.
[h]Significantly different from controls ($p < 0.05$) by Fisher's exact test performed for this review (not analyzed by authors of original study).

Source: Willoughby et al. (2000).

In contrast to the findings in males, F0 and F1 parental female rats exhibited significantly increased mean absolute liver weight in both the mid- and high-dose groups, even when body weight was decreased (Willoughby et al., 2000). Females also showed fewer types of liver lesions (only periacinar hepatocytic vacuolation and hypertrophy) and lower incidences than males. In females, statistically significant increases in liver lesions were found only in the high-dose F0 group. Significantly increased absolute liver weights, with unchanged or decreased body weights, were also observed in the high-dose F1 male and female weanlings ($p < 0.01$) and mid- and high-dose F2 male and female weanlings ($p < 0.05$), although the study authors noted the absence of apparent treatment-related morphological liver changes in the pups.

Willoughby et al. (2000) considered that the male rats exhibited a biphasic hepatic response to D911P treatment, as demonstrated by dose-related increased liver weight in male F1 and F2 pups sacrificed at PND 25, but dose-related decreased liver weight and histopathological evidence of liver damage in the adult male rats sacrificed after weaning of their pups. These observations were considered by the researchers to be indicative of an initial increase in liver weight associated with hypertrophy giving way, as the animals matured, to a decrease in liver weight accompanied by degenerative lesions. The lack of liver weight decrease and milder histopathologic liver lesions in the females were considered by the researchers to be evidence that the female rats were less sensitive to D911P-induced hepatotoxicity.

Organ weight data for selected other organs are shown in Tables B.5 and B.6. High-dose parental male rats (F0 and/or F1) exhibited significant decreases in absolute weights of the adrenal gland, spleen, kidney, epididymides, prostate, and seminal vesicles, and significant increases in relative weights of the epididymides, seminal vesicles, and testes (Willoughby et al., 2000). These changes are consistent with the treatment-related depressed terminal body weight observed in the high-dose parental males of both generations. However, lower adrenal gland weight was also noted in mid-dose F1 males (8% lower than controls) in the absence of a significant effect on body weight.

Table B.5. Selected Mean Organ Weights for Sprague-Dawley Rats Receiving D911P from the Diet for Two Generations								
Dietary D911P concentration (percent)	**0**	**0.1**	**0.5**	**2.0/1.0[a]**	**0**	**0.1**	**0.5**	**1.0**
Parental males	**F0**				**F1**			
Number of animals	27	28	28	28	28	28	28	27
Terminal body weight (g)	639 ± 71[b]	653 ± 70	625 ± 71	517 ± 69[c]	611 ± 72	621 ± 86	634 ± 82	538 ± 64[c]
Kidney								
Absolute (g)	4.33 ± 0.51	4.42 ± 0.44	4.38 ± 0.53	3.85 ± 0.52[c]	4.13 ± 0.68[d]	4.04 ± 0.53	4.31 ± 0.68	3.76 ± 0.38
Relative (%)	0.68 ± 0.05	0.68 ± 0.07	0.70 ± 0.06	0.75 ± 0.06[c]	0.67 ± 0.07[d]	0.65 ± 0.06	0.68 ± 0.07	0.70 ± 0.07[e]
Spleen (g [×10])	8.64 ± 1.32	8.85 ± 2.00	8.21 ± 1.15	7.59 ± 1.06[c]	8.64 ± 1.68	8.53 ± 1.14	8.55 ± 1.98	7.43 ± 1.27[c]
Thymus (g [×10])	3.28 ± 0.65	3.27 ± 1.02	3.40 ± 1.30	3.18 ± 1.07	3.64 ± 0.96	3.71 ± 0.88	3.75 ± 1.01	3.22 ± 0.96
Adrenal gland (g [×10])	0.54 ± 0.13	0.48 ± 0.15	0.47 ± 0.12	0.45 ± 0.11[e]	0.61 ± 0.12	0.56 ± 0.12	0.56 ± 0.07[e]	0.50 ± 0.08[c]
Parental females	**F0**				**F1**			
Number of animals	24	23	22	23	26	23	23	24
Terminal body weight (g)	351 ± 28	356 ± 27	342 ± 20	337 ± 24	341 ± 31	343 ± 34	333 ± 23	325 ± 24[c]
Kidney								
Absolute (g)	3.07 ± 0.38	3.02 ± 0.25	3.04 ± 0.30	2.94 ± 0.21	2.91 ± 0.36	2.77 ± 0.27	2.78 ± 0.21	2.86 ± 0.28
Relative (%)	0.88 ± 0.09	0.85 ± 0.06	0.89 ± 0.09	0.88 ± 0.07	0.86 ± 0.06	0.81 ± 0.07	0.83 ± 0.05	0.88 ± 0.07[e]
Spleen (g [×10])	6.26 ± 0.99	6.21 ± 1.06	5.83 ± 0.74	5.37 ± 0.88[c]	6.63 ± 0.92	6.36 ± 0.96	5.88 ± 0.80[c]	5.35 ± 0.72[c]
Thymus (g [×10])	2.28 ± 0.59	1.97 ± 0.61	1.84 ± 0.65	1.75 ± 0.66[e]	2.50 ± 0.72	2.32 ± 0.49	2.32 ± 0.86	1.75 ± 1.14[e]
Adrenal gland (g [×10])	0.88 ± 0.17	0.88 ± 0.14	0.79 ± 0.13	0.69 ± 0.13[c]	0.87 ± 0.11	0.82 ± 0.11	0.77 ± 0.11[c]	0.64 ± 0.12[c]

[a]The D911P concentration in the food of F0 rats was 2.0% during the first 6 treatment weeks; reduced to 1.0% in the high-dose groups for remainder of study.
[b]Mean ± standard deviation.
[c]Significantly different from controls ($p < 0.01$) by Behrens-Fisher or Dunnett's test.
[d]n=27.
[e]Significantly different from controls ($p < 0.05$) by Behrens-Fisher or Dunnett's test.
[e]Significantly different from controls ($p < 0.05$) by Fisher's exact test.

Source: Willoughby et al. (2000).

Table B.6. Reproductive Organ Weight Data for Male and Female F0 and F1 Parental Sprague-Dawley Rats Exposed to D911P in the Diet

	F0 Males				F1 Males			
Dietary D911P concentration (percent)	0	0.1	0.5	2.0/1.0[a]	0	0.1	0.5	1.0
Number of animals	27	28	28	28	28	28	28	27
Terminal body weight (g)	639 ± 71[b]	653 ± 70	625 ± 71	517 ± 69[c]	611 ± 72	621 ± 86	634 ± 82	538 ± 64[c]
Absolute organ weight (g)								
Epididymides	1.34 ± 0.12	1.32 ± 0.09	1.29 ± 0.13	1.26 ± 0.10[d]	1.32 ± 0.10	1.26 ± 0.16[e]	1.30 ± 0.09	1.23 ± 0.17[d]
Prostate (×10)	6.53 ± 1.69	6.49 ± 1.83	6.52 ± 1.77	5.55 ± 1.05[d]	6.00 ± 1.98	5.52 ± 1.39	5.79 ± 1.61	5.20 ± 1.21
Seminal vesicles	2.49 ± 0.29	2.66 ± 0.26[d]	2.56 ± 0.46	2.19 ± 0.33[c]	2.35 ± 0.30	2.36 ± 0.35[e]	2.28 ± 0.27	2.05 ± 0.28[c]
Testes	3.84 ± 0.42	3.82 ± 0.36	3.75 ± 0.40	3.75 ± 0.30	3.78 ± 0.32	3.85 ± 0.59[e]	3.75 ± 0.31	3.67 ± 0.63
Relative organ weight (g)								
Epididymides	0.21 ± 0.02	0.20 ± 0.03	0.21 ± 0.03	0.25 ± 0.03[c]	0.22 ± 0.03	0.21 ± 0.03[e]	0.21 ± 0.03	0.23 ± 0.04
Prostate	0.10 ± 0.03	0.10 ± 0.03	0.10 ± 0.02	0.11 ± 0.02	0.09 ± 0.03	0.09 ± 0.02	0.09 ± 0.03	0.10 ± 0.03
Seminal vesicles	0.39 ± 0.05	0.41 ± 0.06	0.42 ± 0.10	0.43 ± 0.07[d]	0.39 ± 0.07	0.39 ± 0.06[e]	0.37 ± 0.05	0.39 ± 0.07
Testes	0.60 ± 0.07	0.59 ± 0.09	0.61 ± 0.08	0.73 ± 0.09[c]	0.63 ± 0.08	0.62 ± 0.12[e]	0.60 ± 0.08	0.70 ± 0.16[d]
	F0 Females				F1 Females			
Dietary D911P concentration (percent)	0	0.1	0.5	2.0/1.0[a]	0	0.1	0.5	1.0
Number of animals	24	23	22	23	26	23	23	24
Terminal body weight (g)	351 ± 28[b]	356 ± 27	342 ± 20	337 ± 24	341 ± 31	343 ± 34	333 ± 23	325 ± 24[c]
Absolute organ weight (g)								
Ovaries (×10)	1.10 ± 0.22	1.21 ± 0.20	1.11 ± 0.19	0.98 ± 0.21	1.10 ± 0.15	1.17 ± 0.16	1.11 ± 0.16	0.98 ± 0.20[f]
Uterus + cervix	0.53 ± 0.11	0.53 ± 0.11	0.53 ± 0.18	0.41 ± 0.10[c]	0.52 ± 0.13	0.46 ± 0.13	0.50 ± 0.13	0.43 ± 0.15
Relative organ weight (g)								
Ovaries (×100)	3.15 ± 0.67	3.41 ± 0.52	3.25 ± 0.55	2.91 ± 0.60	3.19 ± 0.41	3.45 ± 0.49	3.34 ± 0.41	3.02 ± 0.50[f]
Uterus + cervix	0.15 ± 0.03	0.15 ± 0.04	0.16 ± 0.06	0.12 ± 0.03[c]	0.15 ± 0.04	0.15 ± 0.04	0.15 ± 0.04	0.13 ± 0.05

[a]The D911P concentration in the food of F0 rats was 2.0% during the first 6 treatment weeks; reduced to 1.0% in the high-dose groups for remainder of study.
[b]Mean ± standard deviation.
[c]Significantly different from controls ($p < 0.01$) by Behrens-Fisher or Dunnett's test.
[d]Significantly different from controls ($p < 0.05$) by Behrens-Fisher or Dunnett's test.
[e]n=27.
[f]n=23.

Source: Willoughby et al. (2000).

High-dose F0 and F1 parental females exhibited significantly decreased absolute weights of adrenal gland, spleen, thymus, and uterus + cervix (F0 only; non-significant decrease of similar magnitude in F1). Absolute adrenal and spleen weights were also reduced in mid-dose F1 parental females. The decreases in organ weights in females occurred despite only small decreases in body weight in these groups (significant only in the high-dose F1). In addition to the decrease in absolute weight, uterus + cervix weight in high-dose F0 females was decreased relative to body weight as well. Relative weights were not reported for the other organs.

Spermatid counts in all treated groups were significantly higher than controls in the F0 generation. Pathological findings included a slight dose-related increase in the number of small epididymides (0/28, 0/28, 1/28, 2/28; control, low-, mid-, high-dose) and small, dark, flaccid testes (0/28, 0/28, 1/28, 2/28; control, low-, mid-, high-dose) in the F0 generation. A dose-related decrease in the number of dilated uterine glands (F0) and dilated uteri (F0, F1) was also reported. Histopathological evaluations of reproductive organs and tissues from F0 and F1 male and female rats and additional testicular and epididymal assessments of sperm count and quality in F0 and F1 males revealed no additional evidence of treatment-related effects.

The study authors stated that no organs other than the liver exhibited any macroscopic or histopathological changes considered to be related to D911P treatment, but did not specifically state whether kidney, spleen, thymus, and adrenal glands were included in histopathological evaluations, although all were collected (Willoughby et al., 2000). Testicular and epididymal assessments of sperm quality in F0 and F1 males revealed no additional evidence of treatment-related effects.

In summary, increased incidences of pathologic liver lesions were observed in F0 and F1 parental male rats administered D911P in the diet at concentrations ≥0.5% for two generations (Willoughby et al., 2000). These effects were accompanied by increased palmitoyl CoA oxidase in the F1 parental males at the same doses and decreased absolute liver and body weights in high-dose parental males of both generations. Female rats were less sensitive, showing only increases in absolute liver weight without lesions at the 0.5% level and significant lesion increases only in the F0 generation at the high dose. No effects of any type were observed at the 0.1% level in parental males or females. For systemic toxicity, these results support the selection of the 0.1% dietary level (approximately 88–117 mg/kg-day) as a NOAEL and the 0.5% dietary level (approximately 444–614 mg/kg-day) as a LOAEL based on liver lesions in the parental male rats. Females were less sensitive, with a NOAEL of 0.5% (approximately 479–

623 mg/kg-day) and LOAEL of 1.0% (approximately 1,389 mg/kg-day based on the F0 generation) based on liver lesions.

High-dose F2 male and female pups exhibited significantly lower body weights than respective controls during PNDs 14–25. Although this effect was also observed in mid-dose F2 female pups at PND 14, it was not seen at other PND time points in this group. The D911P treatment-related effects on pup body weight occurred at doses that also resulted in depressed mean maternal body weight during the lactation period and may indicate an effect on the milk production in underweight lactating dams. However, the effects on pup body weight were not seen during the early lactation period and became evident during the latter stages of the lactational period during which time the pups were beginning to consume solid food, which provides support to a possible systemic toxicity effect in the pups, particularly in light of the finding that the effect persisted for 4 days following the termination of lactation. Pup sexual maturation (preputial separation) was slightly delayed (by one day) in the highest dose of D911P, but the difference was not statistically significant. There were no indications of D911P treatment-related effects on other developmental parameters assessed. Based on the lack of apparent D911P treatment-related developmental toxicity, the 1% D911P dietary level (approximate doses of 1,238–1,510 and 1,264–1,389 mg/kg-day for the parental males and females, respectively) is a NOAEL for developmental effects.

Fulcher et al. (2001)

Systemic and developmental effects of oral D911P were assessed in a study in which timed-pregnant Sprague-Dawley rats (22/group) were administered D911P (in olive oil) at 0, 250, 500, or 1,000 mg/kg-day by gavage (5 mL/kg) between GDs 1 and 19 (Fulcher et al., 2001). The dams were observed for clinical signs, body weights, and food consumption. Following sacrifice on GD 20, the dams were examined grossly for signs of treatment-related effects. Ovaries and uteri were removed and assessed for gravid uterine weight, number of corpora lutea, numbers of implantation sites, and number and distribution of fetuses in each uterine horn. Fetuses were weighed, sexed, and examined for external abnormalities. Half of each litter was subjected to visceral and skeletal examinations; the remaining fetuses were prepared for serial sectioning.

Clinical signs in the dams were limited to salivation, stained fur, and hair loss (Fulcher et al., 2001). Increased salivation was observed sporadically in all dams after dosing, particularly high-dose dams, and was considered by the researchers to reflect distaste for the dosing

formulation. Staining of the fur and hair loss were noted in all dose groups, including controls, and were thought to have been related to the use of olive oil vehicle. No gross effects were seen in the dams at necropsy. All dams were pregnant. Maternal body weight, body weight gain, and food consumption were similar in all D911P-treatment groups and vehicle controls. Pre- and post-implantation losses were unaffected by treatment. There were no significant treatment-related effects on resorbed litters, number of live litters, gravid uterus weight, number of corpora lutea, number of implantation sites/dam, number of resorptions/dam, sex ratio, placental weight, litter weight, or percentages of litters with gross abnormalities. Fetal body weights were slightly increased in high dose males and overall and significantly increased in high dose females. Visceral and skeletal examinations of fetuses revealed increased numbers of high-dose fetuses/litter exhibiting dilated renal pelvis and increased numbers of mid- and high-dose fetuses/litter with supernumerary lumbar ribs (Table B.7). Significantly positive trend tests were reported for each variation. Treatment-related increases in the numbers of cervical ribs or complete 14th ribs were not demonstrated in this study (on a litter or fetus-basis; data not shown).

Table B.7. Selected Fetal Observations Following Administration of D911P to Sprague-Dawley Rat Dams by Gavage During Gestation (GDs 1–19)

	D911P dose (mg/kg-day)			
	0	**250**	**500**	**1,000**
Fetal weight – females (g ± SD)	3.53 ± 0.22	3.66 ± 0.21	3.60 ± 0.22	3.72 ± 0.20[d]
Fetal weight – males (g ± SD)	3.78 ± 0.23	3.86 ± 0.19	3.82 ± 0.27	3.93 ± 0.26
Fetal weight – comb. M&F (g ± SD)	3.66 ± 0.21	3.76 ± 0.20	3.70 ± 0.23	3.83 ± 0.22
Fetal Exams				
Fetuses examined	168	158	158	157
Litters examined	22	22	22	21
Dilated renal pelvis				
Number of fetuses	2	7	2	12
Number of litters	2	3	1	5
Percent affected fetuses per litter	1	4.1	1.3	7.9[a,b]
Supernumerary lumbar ribs				
Number of fetuses	23	24	45	40
Number of litters	13	10	17	14
Percent affected fetuses per litter	13.6	15.9	28.2[c]	26.7[a,b]

[a]Significantly different from control ($p < 0.05$, Wald χ^2 test).
[b]Significant for trend ($p < 0.01$, logistic regression).
[c]Significantly different from control ($p < 0.01$, Wald χ^2 test).
[d]Significantly different from control ($p < 0.01$).

Source: Fulcher et al. (2001).

The study of Fulcher et al. (2001) identified a NOAEL of 1,000 mg/kg-day for maternal effects. For developmental effects, this study identified a NOAEL of 250 mg/kg-day and a

LOAEL of 500 mg/kg-day (increased incidence of supernumerary lumbar ribs in the fetuses of rat dams administered D911P by gavage during gestation).

Brown et al. (1970)

A group of CFE rats (8/sex) was administered undiluted D911P at a dose of 5 mL/kg (4,800 mg/kg based on a specific gravity of 0.96 [BASF Corporation, 2009]) by gavage once per day for 7 consecutive days and sacrificed on the eighth day for histopathological examinations (Brown et al., 1970). A group of untreated controls (20/sex) was included in the study. There were no deaths and no overt clinical signs of toxicity other than what the study authors called "general depression" (no additional description). Histopathological examinations of major viscera revealed periportal cytoplasmic vacuolation in the livers of "some" rats. No additional details were available in the study report.